(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 February 2003 (06.02.2003)

PCT

(10) International Publication Number
WO 03/010141 A2

(51) International Patent Classification[7]: C07D 209/00

(21) International Application Number: PCT/CA02/01128

(22) International Filing Date: 18 July 2002 (18.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/307,674 25 July 2001 (25.07.2001) US
60/338,061 7 December 2001 (07.12.2001) US

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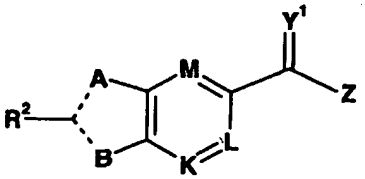
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: VIRAL POLYMERASE INHIBITORS



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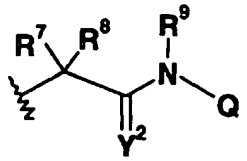

(II)

(57) Abstract: An isomer, enantiomer, diastereoisomer or tautomer of a compound, represented by formula I: wherein: A is O, S, NR^1, or CR^1, wherein R^1 is defined herein; represents either a single or a double bond;R^2 is selected from: H, halogen, R^{21}, OR^{21}, SR^{21}, $COOR^{21}$,$SO_2N(R^{22})_2$, $N(R^{22})_2$, , $CON(R^{22})_2$,$NR^{22}C(O)R^{22}$ or $NR^{22}C(O)NR^{22}$ wherein R^{21} and each R^{22} is defined herein; B is NR^3 or CR^3, with the proviso that one of A or B is either CR^1 or CR^3, wherein R^3 is defined herein; K is N or CR^4, wherein R^4 is defined herein; L is N or CR^5, wherein R^5 has the same definition as R^4; M is N or CR^7, wherein R^7 has the same definition as R^4; Y^1 is O or S; Z is $N(R^{6a})R^6$ or OR^6, wherein R^{6a} is H or alkyl or $NR^{61}R^{62}$ wherein R^{61} and R^{62} are defined herein; and R^6 is H, alkyl, cycloalkyl, alkenyl, Het, alkyl-aryl, alkyl-Het;or R^6 is wherein R^7 and R^8 and Q are as defined herein; Y^2 is O or S; R^9 is H, (C_{1-6} alkyl), (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, Het, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-Het, all of which optionally substituted with R^{90}; or R^9 is covalently bonded to either of R^7 or R^8 to form a 5- or 6-membered heterocycle; a salt or a derivative thereof, as an inhibitor of HCV NS5B polymerase.

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VIRAL POLYMERASE INHIBITORS

TECHNICAL FIELD OF THE INVENTION

The invention relates to inhibitors of RNA dependent RNA polymerases, particularly those viral polymerases within the Flaviviridae family, more particularly to HCV polymerase.

BACKGROUND OF THE INVENTION

About 30,000 new cases of hepatitis C virus (HCV) infection are estimated to occur in the United States each year (Kolykhalov, A.A.; Mihalik, K.; Feinstone, S.M.; Rice, C.M.; 2000; *J. Virol.* **74**: 2046-2051). HCV is not easily cleared by the hosts' immunological defences; as many as 85% of the people infected with HCV become chronically infected. Many of these persistent infections result in chronic liver disease, including cirrhosis and hepatocellular carcinoma (Hoofnagle, J.H.; 1997; *Hepatology* **26**: 15S-20S*). There are an estimated 170 million HCV carriers world-wide, and HCV-associated end-stage liver disease is now the leading cause of liver transplantation. In the United States alone, hepatitis C is responsible for 8,000 to 10,000 deaths annually. Without effective intervention, the number is expected to triple in the next 10 to 20 years. There is no vaccine to prevent HCV infection. Prolonged treatment of chronically infected patients with interferon or interferon and ribavirin is the only currently approved therapy, but it achieves a sustained response in fewer than 50% of cases (Lindsay, K.L.; 1997; *Hepatology* **26**: 71S-77S*, and Reichard, O.; Schvarcz, R.; Weiland, O.; 1997 *Hepatology* **26**: 108S-111S*).

HCV belongs to the family *Flaviviridae*, genus *hepacivirus*, which comprises three genera of small enveloped positive-strand RNA viruses (Rice, C.M.; 1996; "*Flaviviridae*: the viruses and their replication"; pp. 931-960 in *Fields Virology*; Fields, B.N.; Knipe, D.M.; Howley, P.M. (eds.); Lippincott-Raven Publishers, Philadelphia Pa. *). The 9.6 kb genome of HCV consists of a long open reading frame (ORF) flanked by 5' and 3' non-translated regions (NTR's). The HCV 5' NTR is 341 nucleotides in length and functions as an internal ribosome entry site for cap-independent translation initiation (Lemon, S.H.; Honda, M.; 1997; *Semin. Virol.* **8**: 274-288). The HCV polyprotein is cleaved co- and post-translationally into at least 10 individual polypeptides (Reed, K.E.; Rice, C.M.; 1999; *Curr. Top. Microbiol. Immunol.* **242**: 55-84*). The structural proteins result from signal peptidases in the N-

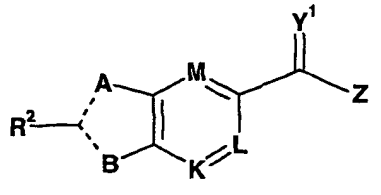
terminal portion of the polyprotein. Two viral proteases mediate downstream cleavages to produce non-structural (NS) proteins that function as components of the HCV RNA replicase. The NS2-3 protease spans the C-terminal half of the NS2 and the N-terminal one-third of NS3 and catalyses *cis* cleavage of the NS2/3 site. The same portion of NS3 also encodes the catalytic domain of the NS3-4A serine protease that cleaves at four downstream sites. The C-terminal two-thirds of NS3 is highly conserved amongst HCV isolates, with RNA-binding, RNA-stimulated NTPase, and RNA unwinding activities. Although NS4B and the NS5A phosphoprotein are also likely components of the replicase, their specific roles are unknown. The C-terminal polyprotein cleavage product, NS5B, is the elongation subunit of the HCV replicase possessing RNA-dependent RNA polymerase (RdRp) activity (Behrens, S.E.; Tomei, L.; DeFrancesco, R.; 1996; *EMBO J.* **15**: 12-22*; and Lohmann, V.; Körner, F.; Herian, U.; Bartenschlager, R.; 1997; *J. Virol.* **71**: 8416-8428*). It has been recently demonstrated that mutations destroying NS5B activity abolish infectivity of RNA in a chimp model (Kolykhalov, A.A.; Mihalik, K.; Feinstone, S.M.; Rice, C.M.; 2000; *J. Virol.* **74**: 2046-2051*).

The development of new and specific anti-HCV treatments is a high priority, and virus-specific functions essential for replication are the most attractive targets for drug development. The absence of RNA dependent RNA polymerases in mammals, and the fact that this enzyme appears to be essential to viral replication, would suggest that the NS5B polymerase is an ideal target for anti-HCV therapeutics.
WO 00/06529 reports inhibitors of NS5B which are α, γ-diketoacids.
WO 00/13708, WO 00/10573, WO 00/18231, and WO 01/47883 report inhibitors of NS5B proposed for treatment of HCV.

SUMMARY OF THE INVENTION

It is therefore an object of the invention to provide a novel series of compounds having improved inhibitory activity against HCV polymerase.

In a first aspect of the invention, there is provided an isomer, enantiomer, diastereoisomer or tautomer of a compound, represented by formula I:



(I)

wherein:

A is O, S, NR^1, or CR^1, wherein R^1 is selected from the group consisting of: H, (C_{1-6})alkyl optionally substituted with:

-halogen, OR^{11}, SR^{11} or $N(R^{12})_2$, wherein R^{11} and each R^{12} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**, said aryl or **Het** optionally substituted with R^{10}; or

both R^{12} are covalently bonded together and to the nitrogen to which they are both attached to form a 5, 6 or 7-membered saturated heterocycle;

----- represents either a single or a double bond;

R^2 is selected from: halogen, R^{21}, OR^{21}, SR^{21}, $COOR^{21}$, $SO_2N(R^{22})_2$, $N(R^{22})_2$, , $CON(R^{22})_2$, $NR^{22}C(O)R^{22}$ or $NR^{22}C(O)NR^{22}$ wherein R^{21} and each R^{22} is independently H, (C_{1-6})alkyl, haloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, (C_{2-6})alkynyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**, said R^{21} and R^{22} being optionally substituted with R^{20};

or both R^{22} are bonded together to form a 5, 6 or 7-membered saturated heterocycle with the nitrogen to which they are attached;

B is NR^3 or CR^3, with the proviso that one of **A** or **B** is either CR^1 or CR^3, wherein R^3 is selected from (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, (C_{5-7})cycloalkenyl, (C_{6-10})bicycloalkyl, (C_{6-10})bicycloalkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**,

said alkyl, cycloalkyl, cycloakenyl, bicycloalkyl, bicycloalkenyl, aryl, **Het**, alkyl-aryl and alkyl-**Het** being optionally substituted with from 1 to 4 substituents selected from: halogen, or

a) (C_{1-6})alkyl optionally substituted with:

- OR^{31} or SR^{31} wherein R^{31} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl,

(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or

- $N(R^{32})_2$ wherein each R^{32} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{32} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

b) OR^{33} wherein R^{33} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**;

c) SR^{34} wherein R^{34} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; and

d) $N(R^{35})_2$ wherein each R^{35} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{35} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

K is N or CR^4, wherein R^4 is H, halogen, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or R^4 is OR^{41} or SR^{41}, COR^{41} or $NR^{41}COR^{41}$ wherein each R^{41} is independently H, (C_{1-6})alkyl), (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or R^4 is $NR^{42}R^{43}$ wherein R^{42} and R^{43} are each independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, or both R^{42} and R^{43} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

L is N or CR^5, wherein R^5 has the same definition as R^4 defined above;

M is N or CR^7, wherein R^7 has the same definition as R^4 defined above;

Y^1 is O or S;

Z is OR^6 wherein R^6 is C_{1-6}alkyl substituted with:

- 1 to 4 substituents selected from: OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$,

C(=NH)NH(C_{1-6})alkyl or C(=NH)NHCO(C_{1-6})alkyl; or

- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is (C_{1-6}alkyl) substituted with R^{150}, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, SO_3H, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl,

or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};
or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{124} is OH or $O(C_{1-6}$alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is (C_{1-6})alkyl substituted with R^{150}, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, all of which being optionally substituted with R^{150};

wherein R^{150} is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano, azido or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted

with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$, or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to

which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

or **Z** is OR^6 wherein R^6 is (C_{1-6}alkyl)aryl substituted with:

- 1 to 4 substituents selected from: OPO_3H, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6})alkyl substituted with R^{150a}, haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, said haloalkyl, cycloalkyl, spirocycloalkyl, alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with R^{150}, wherein R^{150a} is the same as R^{150} but is not $COOR^{150b}$, $N(R^{150b})_2$, $NR^{150b}C(O)R^{150b}$, OR^{150b}, SR^{150b}, SO_2R^{150b}, $SO_2N(R^{150b})_2$, wherein R^{150b} is H or unsubstituted C_{1-6}alkyl;

b) OR^{104} wherein R^{104} is (C_{1-6}alkyl) substituted with R^{150}, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108a}, $SO_2N(R^{108a})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150}, wherein R^{108a} is the same as R^{108} but is not H or unsubstituted C_{1-6}alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl,

or R^{112} is also $COOR^{115}$ or SO_2R^{115a} wherein R^{115} is H, (C_{1-6})alkyl, (C_{3-}

$_7$)cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{115a} is the same as R^{115} but is not H or unsubstituted alkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each (C_{1-6})alkyl substituted with R^{150}, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is (C_{1-6})alkyl substituted with R^{150}, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is (C_{1-6})alkyl substituted with R^{150}, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{3-}

$_{7}$)cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, provided that when R^{129} is H or unsubstituted alkyl, R^{130} is not H or unsubstituted alkyl,

or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** all of which being optionally substituted with R^{150}; and

wherein R^{150} is

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido;
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-}

$_6$)alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}; and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein, R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above;

or **Z** is OR^6 wherein R^6 is, (C_{3-6})cycloalkyl, (C_{2-6})alkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-**Het**, wherein said cycloalkyl, alkenyl, aryl, **Het** or alkyl-**Het**, is optionally substituted with R^{60};

or **Z** is $N(R^{6a})R^6$, wherein R^{6a} is H or (C_{1-6}alkyl) and

R^6 is (C_{1-6})alkyl optionally substituted with:

- 1 to 4 substituents selected from: OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl substituted with R^{150a}, haloalkyl substituted with R^{150}, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150}, wherein R^{150a} is the same as R^{150} but is not halogen, OH, O(C_{1-6}alkyl), COOH, COO(C_{1-6}alkyl), NH_2, NH(C_{1-6}alkyl) and N(C_{1-6}alkyl)$_2$;

b) OR^{104} wherein R^{104} is (C_{1-6}alkyl) substituted with R^{150}, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, SO_3H, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is

independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het**, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-}

$_6$alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is (C_{1-6})alkyl substituted with R^{150}, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** all of which being optionally substituted with R^{150}, wherein R^{150} is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano, azido or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-}

$_7$)cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle

being optionally substituted with R^{160};

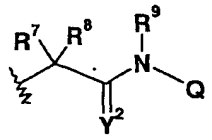
j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above;

or **Z** is $N(R^{6a})R^6$ wherein R^{6a} is as defined above and R^6 is (C_{3-6})cycloalkyl, (C_{2-6})alkenyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkyl, cycloalkyl, alkenyl, aryl, **Het**, alkyl-aryl, or alkyl-**Het**, are all optionally substituted with R^{60};

or **Z** is OR^6 or $N(R^{6a})R^6$ wherein R^{6a} is as defined above and R^6 is:



wherein R^7 and R^8 are each independently H, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** are optionally substituted with R^{70}; or

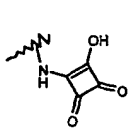
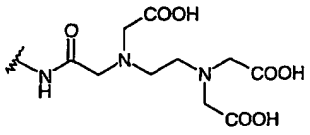
R^7 and R^8 are covalently bonded together to form second (C_{3-7})cycloalkyl or a 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S; or when **Z** is $N(R^{6a})R^6$, either of R^7 or R^8 is covalently bonded to R^{6a} to form a

nitrogen-containing 5-or 6-membered heterocycle;

Y^2 is O or S;

R^9 is H, (C_{1-6} alkyl), (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**, all of which optionally substituted with R^{90}; or
R^9 is covalently bonded to either of R^7 or R^8 to form a 5- or 6-membered heterocycle;

Q is a 6- or 10-membered aryl, **Het**, (C_{1-6}) alkyl-aryl, (C_{1-6}) alkyl-**Het**, (C_{1-6}) alkyl-CONH-aryl or (C_{1-6}) alkyl-CONH-**Het**, all of which being optionally substituted with:



, or R^{100};

or a salt or a derivative thereof;

wherein **Het** is defined as 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, or a 9- or 10-membered heterobicycle having 1 to 5 heteroatoms selected from O, N and S; and

R^{10}, R^{20}, R^{60}, R^{70}, R^{90} and R^{100} is each defined as:

- 1 to 4 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is

independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are

covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150}; and

wherein R^{150} is defined as:

- 1 to 3 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl,

aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160}, or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

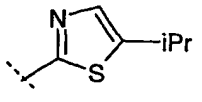
j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SR^{161}, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle,

or a salt thereof,

with the proviso that, when **A** is CH, R^2 is phenyl or N-butyl, **B** is NR^3, R^3 is Me, **K** is

CH, **L** is CH, **M** is CH, Y^1 is O, and **Z** is NHR^6, then R^6 is not 

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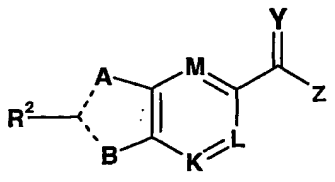
Alternatively, in a first aspect of the invention, there is provided a compound represented by Formula Ia:



(Ia)

wherein:

A is O, S, NR^1, or CR^1;

B is NR^3 or CR^3;

R^1 is selected from the group consisting of: H, (C_{1-6})alkyl, benzyl, $(C_{1-6}$ alkyl)-$(C_{6-10}$aryl), $(C_{1-6}$ alkyl)-5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, and 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N and S,

wherein said benzyl and said heteroatom are optionally substituted with from 1 to 4 substituents selected from the group consisting of: COOH, $COO(C_{1-6}$ alkyl), halogen, and $(C_{1-6}$ alkyl);

R^2 is selected from the group consisting of: H, halogen, (C_{1-6})alkyl; (C_{3-7})cycloalkyl, phenyl, 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, pyridine-N-oxide , and 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S,

said phenyl, heterocycle and heterobicycle being optionally substituted with from 1 to 4 substituents selected from the group consisting of: halogen, $C(halogen)_3$, (C_{1-6})alkyl, OH, $O(C_{1-6}$ alkyl), NH_2, and $N(C_{1-6}$ alkyl$)_2$;

R^3 is selected from the group consisting of: 5-, 6- or 7-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, norbornane, (C_{3-7})cycloalkyl and (C_{3-7})cycloalkyl-$(C_{1-6}$ alkyl);

M is N, CR^4, or COR^5, wherein R^4 is selected from the group consisting of: H,

halogen, and (C_{1-6} alkyl); and R^5 is selected from the group consisting of: H and (C_{1-6} alkyl);

K and **L** is N or CH;

----- represents either a single or a double bond;

Y is O or S;

Z is OR^6 or NR^6R^{6a}

R^6 is selected from the group consisting of: H, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-6})alkyl, (C_{6-10})aryl, (C_{6-10})aryl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-6})cycloalkyl(C_{2-6})alkenyl, (C_{6-10})aryl(C_{2-6})alkenyl, N{(C_{1-6}) alkyl}$_2$, NHCOO(C_{1-6})alkyl(C_{6-10})aryl, NHCO(C_{6-10})aryl, (C_{1-6})alkyl-5- or 6-atom heterocycle, having 1 to 4 heteroatoms selected from O, N and S, and 9- or 10-atom heterobicycle having 1 to 4 heteroatoms selected from O, N and S;

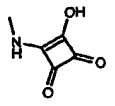
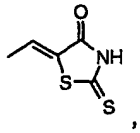
wherein said alkyl, cycloalkyl, aryl, alkenyl, heterocycle are all optionally substituted with from 1 to 4 substituents selected from: OH, COOH, COO(C_{1-6})alkyl, (C_{1-6})alkyl, (C_{1-6})alkyl-hydroxy, phenyl, benzyloxy, halogen, (C_{2-4})alkenyl, (C_{2-4})alkenyl-(C_{1-6})alkyl-COOH, 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N and S,

wherein said alkyl, cycloalkyl, aryl, alkenyl and heterocycle being optionally substituted with from 1 to 4 substituents selected from: (C_{1-6} alkyl), CF_3, OH, COOH, NHC(C_{1-6}alkyl)$_2$, NHCO(C_{1-6} alkyl), NH_2, NH(C_{1-6} alkyl), and N(C_{1-6} alkyl)$_2$;

9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S, said heterobicycle being optionally substituted with from 1 to 4 substituents selected from:

halogen, OPO_3H, sulfonamido, SO_3H, SO_2CH_3, -$CONH_2$, -$COCH_3$, (C_{1-3})alkyl, (C_{2-4}alkenyl)COOH, tetrazolyl, COOH, -$CONH_2$, triazolyl, OH, NO_2, NH_2, -O(C_{1-6} alkyl)COOH, hydantoin, benzoyleneurea, (C_{1-4})alkoxy, cyano, azido, -O-(C_{1-6})alkyl COOH, -O-(C_{1-6})alkyl COO-(C_{1-6})alkyl, NHCO(C_{1-}

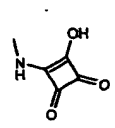
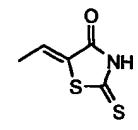
$_6$ alkyl), -NHCOCOOH, -NHCOCONHOH,-NHCOCONH$_2$, -NHCOCONHCH$_3$, -NHCO(C_{1-6})alkyl-COOH, -NHCOCONH(C_{1-6})alkyl-COOH, -NHCO(C_{3-7})cycloalkyl-COOH, -NHCONH(C_{6-10})aryl-COOH, - NHCONH(C_{6-10})aryl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-COOH,- NHCONH(C_{1-6})alkyl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-(C_{2-6})alkenyl-COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-O(C_{1-6})alkyl COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-COOH, -NHCH$_2$COOH, -NHCONH$_2$, -NHCO(C_{1-6})hydroxyalkyl COOH, -OCO(C_{1-6})hydroxyalkyl COOH, (C_{3-6})cycloalkyl COOH,

, -NHCN, -NHCHO, -NHSO$_2$CH$_3$, and -NHSO$_2$CF$_3$;

6- or 10-membered aryl being optionally substituted with from 1 to 4 substituents selected from:

halogen, OPO$_3$H, sulfonamido, SO$_3$H, SO$_2$CH$_3$, -CONH$_2$, -COCH$_3$, (C_{1-3})alkyl, (C_{2-4}alkenyl)COOH , tetrazolyl, COOH, -CONH$_2$, triazolyl, OH, NO$_2$, NH$_2$, -O(C_{1-6} alkyl)COOH, hydantoin, benzoyleneurea, (C_{1-4})alkoxy, cyano, azido, -O-(C_{1-6})alkyl COOH, -O-(C_{1-6})alkyl COO-(C_{1-6})alkyl, NHCO(C_{1-6} alkyl), -NHCOCOOH, -NHCOCONHOH,-NHCOCONH$_2$, -NHCOCONHCH$_3$, -NHCO(C_{1-6})alkyl-COOH, -NHCOCONH(C_{1-6})alkyl-COOH, -NHCO(C_{3-7})cycloalkyl-COOH, -NHCONH(C_{6-10})aryl-COOH, - NHCONH(C_{6-10})aryl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-COOH,- NHCONH(C_{1-6})alkyl-COO(C_{1-6})alkyl, - NHCONH(C_{1-6})alkyl-(C_{2-6})alkenyl-COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-O(C_{1-6})alkyl COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-COOH, -NHCH$_2$COOH, -NHCONH$_2$, -NHCO(C_{1-6})hydroxyalkyl COOH, -OCO(C_{1-6})hydroxyalkyl COOH, (C_{3-6})cycloalkyl COOH,

, -NHCN, -NHCHO, -NHSO$_2$CH$_3$, and

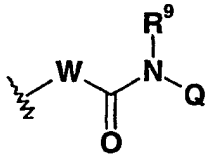
$-NHSO_2CF_3$;

coumarin, (C_{1-6})alkyl-amino, $NH(C_{1-6}$ alkyl), $C(halogen)_3$,

$-NH(C_{2-4})$acyl, $-NH(C_{6-10})$aroyl, $-O(C_{1-6}$alkyl)-**Het**;

R^{6a} is H or (C_{1-6} alkyl) covalently bonded to either R^7 or R^8 to form pyrrolidine;

or **Z** is



wherein

W is CR^7R^8 wherein R^7 and R^8 are each independently H, (C_{1-6} alkyl), (C_{3-7} cycloalkyl), (C_{1-6} alkyl)phenyl, (C_{1-6} alkyl)-(C_{3-7} cycloalkyl), (C_{3-7} cycloalkyl)-(C_{1-6} alkyl), (C_{3-7} cycloalkyl)-(C_{2-4} alkenyl), (C_{1-6} alkyl)-OH, phenyl, CH_2biphenyl, 5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S, 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N, and S, (C_{1-6} alkyl)-5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S, or (C_{1-6} alkyl)-9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N, and S,

or R^7 and R^8 are covalently bonded together to form (C_{3-7} cycloalkyl), 4-, 5- or 6-membered heterocycle having from1 to 4 heteroatoms selected from O, N, and S;

or one of R^7 or R^8 is covalently bonded to R^9 to form a pyrrolidine;

wherein said alkyl, cycloalkyl, heterocycle, heterobicycle, phenyl are optionally substituted with from 1 to 4 substituents selected from the group consisting of: OH, COOH, (C_{1-6} alkyl), (C_{2-4} alkenyl), $CONH_2$, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, NHCOCOOH, $NHCOCON(C_{1-6}$ alkyl)$_2$, $NHCOCONH(C_{1-6}$ alkyl), SH, $S(C_{1-6}$ alkyl), $NHC(=NH)NH_2$, halogen, and $COO(C_{1-6}$alkyl);

R^9 is H or (C_{1-6} alkyl); and

Q is selected from the group consisting of: $(C_{1-3}$alkyl)CONHaryl, 6-, 9-, or 10-membered aryl, biphenyl, 5- or 6-atom heterocycle having 1 to 4 heteroatoms selected from O, N and S, 9- or 10-membered heterobicycle having 1 to 4 heteroatoms selected from O, N and S;

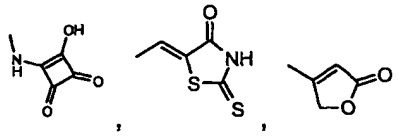
wherein said aryl, biphenyl, heterocycle and heterobicycle are all optionally substituted with from 1 to 4 substituents selected from: OH, COOH, $COO(C_{1-6})$alkyl, (C_{1-6})alkyl, (C_{1-6})alkylCOOH, $(C_{1-6}$ alkyl$)(C_{2-4}$ alkynyl), (C_{1-6})alkyl-hydroxy, phenyl, benzyloxy, halogen, (C_{2-4})alkenyl, (C_{2-4})alkenyl-(C_{1-6})alkyl-COOH, 5- or 6-membered second heterocycle having 1 to 4 heteroatoms selected from O, N and S, NH-5- or 6- membered second heterocycle having 1 to 4 heteroatoms selected from O, N, and S,

wherein said second heterocycle and phenyl being optionally substituted with from 1 to 4 substituents selected from: $(C_{1-6}$ alkyl), CF_3, OH, $(C_{1-6}$alkyl) COOH, $O(C_{1-6}$alkyl)COOH, $(C_{1-6}$alkyl) $COO(C_{1-6}$alkyl), CH_2phenyl, $COO(C_{1-6}$ alkyl), $(C_{1-6}$alkyl)$O(C_{1-6}$alkyl), COOH, $NCH(C_{1-6}$alkyl$)_2$, $NCO(C_{1-6}$ alkyl), NH_2, $NH(C_{1-6}$ alkyl), halogen, and $N(C_{1-6}$ alkyl$)_2$;

halogen, OPO_3H, benzyl, sulfonamido, SH, $SOCH_3$, SO_3H, SO_2CH_3, $S(C_{1-6}$ alkyl)COOH, $-CONH_2$, $-COCH_3$, (C_{1-3})alkyl, $(C_{2-4}$alkenyl)COOH

wherein said alkenyl is optionally substituted with from 1 to 2 $(C_{1-6}$ alkyl) substituents,

$(C_{2-4}$alkenyl$)COO(C_{1-6}$alkyl), tetrazolyl, COOH, triazolyl, OH, NO_2, NH_2, , -$O(C_{1-6}$ alkyl)COOH, hydantoin, benzoyleneurea, (C_{1-4})alkoxy, (C_{1-4})alkoxy$(C_{1-6}$ alkyl)COOH, cyano, azido, -O-(C_{1-6})alkyl COOH, -O-(C_{1-6})alkyl COO-(C_{1-6})alkyl, -NHCOCOOH, -NHCOCONHOH,-$NHCOCONH_2$, $-NHCOCONHCH_3$, -NHCO(C_{1-6})alkyl-COOH, -NHCOCONH(C_{1-6})alkyl-COOH, -NHCO(C_{3-7})cycloalkyl-COOH, -NHCONH(C_{6-10})aryl-COOH, - NHCONH(C_{6-10})aryl-$COO(C_{1-6})$alkyl, - NHCONH(C_{1-6})alkyl-COOH,- NHCONH(C_{1-6})alkyl-$COO(C_{1-6})$alkyl, - NHCONH(C_{1-6})alkyl-(C_{2-6})alkenyl-COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-$O(C_{1-6})$alkyl COOH, - NH(C_{1-6})alkyl-(C_{6-10})aryl-COOH, $-NHCH_2COOH$, $-NHCONH_2$, -NHCO(C_{1-6})hydroxyalkyl COOH, -OCO(C_{1-6})hydroxyalkyl COOH, (C_{3-6})cycloalkyl COOH,



, -NHCN, -NHCHO, $-NHSO_2CH_3$, $-NHSO_2CF_3$, coumarin, (C_{1-6})alkyl-amino, NH$(C_{1-6}$alkyl$)_2$, C(halogen)$_3$, -NH(C_{2-4})acyl, -NH(C_{6-10})aroyl, -CONH$(C_{1-6}$alkyl), -CO(C_{1-6})alkyl-COOH, -CONH(C_{1-6})alkyl-COOH, -CO-NH-alanyl, -CONH(C_{2-4})alkylN$(C_{1-6}$alkyl$)_2$, -CONH(C_{2-4}) alkyl-**Het**,

-CONH(C_{2-4}) alkyl-(COOH)-**Het**, -CONH(C_{1-2} alkyl) (OH)(C_{1-2} alkyl)OH,
-CONH(C_{1-6}) alkyl-COOH, -CONH(C_{6-10} aryl), -CONH-**Het**,
-CONH(C_{6-10}) aryl-COOH, -CONH(C_{6-10}) aryl-COO(C_{1-6}) alkyl,
-CONH(C_{1-6}) alkyl-COO(C_{1-6}) alkyl, -CONH(C_{6-10}) aryl-(C_{1-6})alkyl-COOH, and
-CONH(C_{6-10}) aryl-(C_{2-6})alkenyl-COOH,

or a salt thereof.

In a third aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, as an inhibitor of RNA dependent RNA polymerase activity of the enzyme NS5B, encoded by HCV.

In a fourth aspect of the invention, there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, as an inhibitor of HCV replication.

In a fifth aspect of the invention, there is provided a method of treating or preventing HCV infection in a mammal, comprising administering to the mammal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

In a sixth aspect of the invention, there is provided a pharmaceutical composition for the treatment or prevention of HCV infection, comprising an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

According to a specific embodiment, the pharmaceutical compositions of this invention comprise an additional immunomodulatory agent. Examples of additional immunomodulatory agents include but are not limited to, α-, β-, δ- γ-, and ω-interferons.

According to an alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an antiviral agent. Examples of antiviral agents include, ribavirin and amantadine.

According to another alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise other inhibitors of HCV protease.

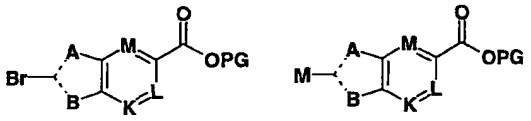
According to yet another alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an inhibitor of other targets in the HCV life cycle, such as helicase, polymerase, metalloprotease or IRES.

In a seventh aspect of the invention, there is provided a use of a compound of formula I, for the manufacture of a medicament for the treatment of HCV infection.

In a eighth aspect of the invention, there is provided a use of a compound of formula I, to prevent HCV infection.

In an ninth aspect of the invention, there is provided a use of a compound of formula I, as an HCV polymerase inhibitor.

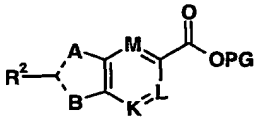
In a tenth aspect of the invention, there is provided an intermediate of formula (1a) or (1b):



1a or 1b

wherein **A, B, K, L**, and **M** are as described herein and **PG** is H or a carboxy protecting group.

In a eleventh aspect of the invention, there is provided a process for producing compounds of formula (iii),

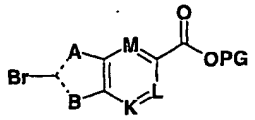


(iii)

wherein **A, R^2, B, K, L, M,** and **PG** are as described herein,

comprising:

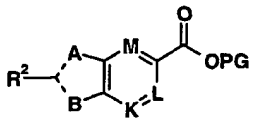
a) coupling, in the presence of a metal catalyst (such as, for example, Pd, Ni, Ru, Cu), a base and an additive (such as a phosphine ligand, Cu salt, Li salt, ammonium salt, CsF) in an appropriate solvent, intermediate (1a)



1a

with R^2-**X**, wherein R^1, R^3, **K**, **L**, **M** and **PG** are as described herein and **X** is (bt not limited to): $Sn(C_{1-6}alkyl)_3$, $Sn(aryl)_3$, metal halide, $B(OH)_2$, and $B(O(C_{1-6})alkyl)_2$ to produce compounds of formula (iii).

In an alternative to the eleventh aspect of the invention, there is provided a process for producing compounds of formula (iii),

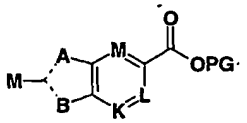


(iii)

wherein **A**, R^2, **B**, **K**, **L**, **M**, and **PG** are as described herein,

comprising:

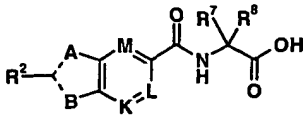
b) coupling, in the presence of a metal catalyst (such as, for example, Pd, Ni, Ru, Cu), a base and an additive (such as a phosphine ligand, Cu salt, Li salt, ammonium salt, CsF) in an appropriate solvent, intermediate (1b)



1b

with R^2-**X'**, wherein **X'** is halide, $OSO_2(C_{1-6}alkyl)$, OSO_2Ar, OSO_2CF_3 and the like, and **M** is a metal such as Li, $Sn(C_{1-6}alkyl)_3$, $Sn(aryl)_3$, $B(OH)_2$, $B(OC_{1-6}alkyl)_2$, metal halide, to produce compounds of formula (iii).

In an thirteenth aspect of the invention, there is provided an intermediate compound represented by formula 1c:



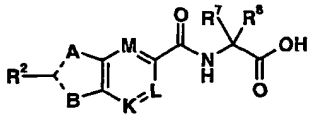
1c

wherein **A**, R^2, **B**, **K**, **L**, **M**, R^7 and R^8 are as defined herein, or a salt, or a derivative

thereof.

In an fourteenth aspect of the invention, there is provided a process for producing compounds of formula I, comprising:

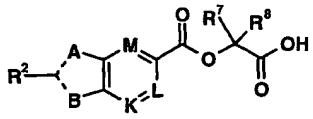
a) coupling, in a mixture containing an aprotic solvent, or no solvent, a coupling agent, and at a temperature of about 20 °C to about 170 °C, and intermediate 1c:



1c

with amine **Q**-NH_2 so as to produce compounds of formula I, wherein **A**, R^2, **B**, R^7, R^8, **Q**, **K**, **L**, and **M** are as defined herein.

In an fifteenth aspect of the invention, there is provided an intermediate compound represented by formula 1d:

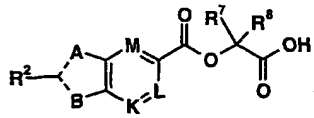


1d

wherein **A**, R^2, **B**, **K**, **L**, **M**, R^7 and R^8 are as defined herein or a salt or a derivative thereof.

In a sixteenth aspect of the invention, there is provided a process for producing compounds of formula I, comprising:

a) coupling, in a mixture containing an appropriate solvent, or no solvent, a coupling agent, and at a temperature of about 20 °C to about 170 °C, and intermediate 1d:



1d

with amine **Q**-NH_2 so as to produce compounds of formula I, wherein **A**, R^2, **B**, R^7, R^8, **Q**, **K**, **L**, and **M** are as defined herein.

In a seventeenth aspect of the invention, there is provided a method of treating or

preventing HCV infection in a mammal, comprising administering to the mammal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in combination with another anti-HCV agent.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The following definitions apply unless otherwise noted:

As used herein, the terms "(C_{1-3}) alkyl", "(C_{1-4}) alkyl" or "(C_{1-6}) alkyl", either alone or in combination with another radical, are intended to mean acyclic straight or branched chain alkyl radicals containing up to three, four and six carbon atoms respectively. Examples of such radicals include methyl, ethyl, propyl, butyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl.

As used herein, the term "(C_{2-6}) alkenyl", either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight chain radical containing two to six carbon atoms.

As used herein, the term (C_{2-6}) alkynyl" either alone or in combination with another group, is intended to mean an unsaturated, acyclic straight chain sp hybridized radical containing 2 to six carbon atoms.

As used herein. the term "(C_{3-7}) cycloalkyl", either alone or in combination with another radical, means a cycloalkyl radical containing from three to seven carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

As used herein, the term "(C_{5-7})cycloalkenyl", either alone or in combination with another radical, means an unsaturated cyclic radical containing five to seven carbon atoms.

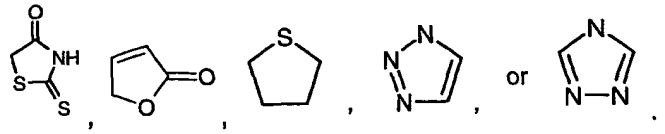
As used herein, the term "carboxy protecting group" defines protecting groups that can be used during coupling and are listed in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1981) and "The Peptides: Analysis, Synthesis, Biology", Vol. 3, Academic Press, New York (1981), the disclosures of which are hereby incorporated by reference.

The α-carboxyl group of the C-terminal residue is usually protected as an ester (CPG) that can be cleaved to give the carboxylic acid. Protecting groups that can be used include: 1) alkyl esters such as methyl, trimethylsilylethyl and *t*-butyl, 2) aralkyl esters such as benzyl and substituted benzyl, or 3) esters that can be cleaved by mild base treatment or mild reductive means such as trichloroethyl and phenacyl esters.

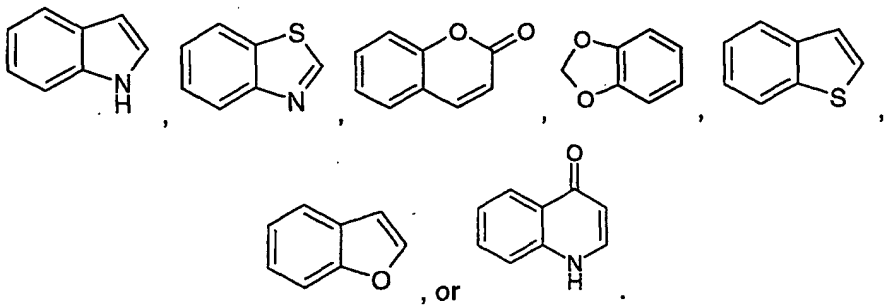
As used herein, the term "aryl", or "6- or 10-membered aryl" either alone or in combination with another radical means aromatic radical containing six or ten carbon atoms, for example phenyl or naphthyl.

As used herein the term heteroatom means O, S or N.

As used herein, the term "heterocycle", either alone or in combination with another radical, means a monovalent radical derived by removal of a hydrogen from a five-, six-, or seven-membered saturated or unsaturated (including aromatic) heterocycle containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur. Furthermore, "heterobicyclic" as used herein, means a heterocycle as defined above fused to one or more other cycle, be it a heterocycle or any other cycle. Examples of such heterocycles include, but are not limited to, pyrrolidine, tetrahydrofuran, thiazolidine, pyrrole, thiophene, coumarin, hydantoin, diazepine, 1H-imidazole, isoxazole, thiazole, tetrazole, piperidine, 1,4-dioxane, 4-morpholine, pyridine, pyridine-N-oxide, pyrimidine, thiazolo[4,5-b]-pyridine, quinoline, or indole, or the following heterocycles:



As used herein, the term "9- or 10-membered heterobicycle" or "heterobicycle" either alone or in combination with another radical, means a heterocycle as defined above fused to one or more other cycle, be it a heterocycle or any other cycle. Examples of such heterobicycles include, but are not limited to, thiazolo[4,5-b]-pyridine, quinoline, or indole, or the following:



As used herein, the term "**Het**" defines a 5- or 6-membered heterocycle having 1 to 4 heteroatoms selected from O, N, and S, or a 9- or 10-membered heterobicycle having 1 to 5 heteroatoms wherever possible, selected from O, N and S.

As used herein, the term "halo" means a halogen atom and includes fluorine, chlorine, bromine and iodine.

As used herein, the term "haloalkyl" is intended to mean an alkyl that is described above in which each hydrogen atom may be successively replaced by a halogen atom, for example CH_2Br or CF_3.

As used herein, the term "metal halide" is intended to mean any metal that is bonded to a halogen atom for use in a metal-catalyzed cross-coupling reaction. Examples of such metal halides include, but are not limited to, -MgCl, -CuCl, or -ZnCl and the like.

As used herein, the term "OH" refers to a hydroxyl group. It is well known to one skilled in the art that hydroxyl groups may be substituted by functional group equivalents. Examples of such functional group equivalents that are contemplated by this invention include, but are not limited to, ethers, sulfhydryls, and primary, secondary or tertiary amines.

As used herein, the term "SH" refers to a sulfhydryl group. It is intended within the scope of the present invention that , whenever a "SH" or "**SR**" group is present, it can also be substituted by any other appropriate oxidation state such as **SOR**, SO_2**R**, or SO_3**R**.

It is intended that the term "substituted" when applied in conjunction with a radical

having more than one moiety such as C_{1-6}alkyl-aryl, or C_{1-6}alkyl-**Het**, such substitution applies to both moieties i.e. both the alkyl and aryl or **Het** moieties can be substituted with the defined substituents.

As used herein, the term "COOH" refers to a carboxylic acid group. It is well known to one skilled in the art that carboxylic acid groups may be substituted by functional group equivalents. Examples of such functional group equivalents that are contemplated by this invention include, but are not limited to, esters, amides, boronic acids or tetrazole.

As used herein, the term "functional group equivalent" is intended to mean an element or a substituted derivative thereof, that is replaceable by another element that has similar electronic, hybridization or bonding properties.

As used herein, the term "metal catalyst" is intended to mean a metal such as palladium (0) or palladium (2) that is bonded to a leaving group for use in a cross-coupling reaction. Examples of such palladium catalysts include, but are not limited to, $Pd(Ph_3)_4$, Pd/C, $Pd(OAc)_2$, $PdCl_2$, and the like. Alternative metals that can catalyze cross-coupling reactions include, but are not limited to: $Ni(acac)_2$, $Ni(OAc)_2$, or $NiCl_2$.

As used herein, the term "derivative" is intended to mean "detectable label", "affinity tag" or "photoreactive group". The term "detectable label" refers to any group that may be linked to the polymerase or to a compound of the present invention such that when the compound is associated with the polymerase target, such label allows recognition either directly or indirectly of the compound such that it can be detected, measured and quantified. Examples of such "labels" are intended to include, but are not limited to, fluorescent labels, chemiluminescent labels, colorimetric labels, enzymatic markers, radioactive isotopes and affinity tags such as biotin. Such labels are attached to the compound or to the polymerase by well known methods. The term "affinity tag" means a ligand (that is linked to the polymerase or to a compound of the present invention) whose strong affinity for a receptor can be used to extract from a solution the entity to which the ligand is attached. Examples of such ligands include biotin or a derivative thereof, a histidine polypeptide, a polyarginine, an amylose sugar moiety or a defined epitope recognizable by a

specific antibody. Such affinity tags are attached to the compound or to the polymerase by well-known methods.

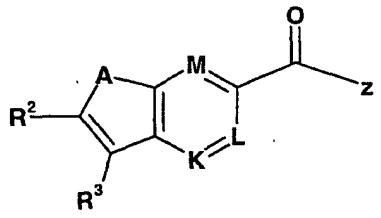
The term "photoreactive group" means a group that is transformed, upon activation by light, from an inert group to a reactive species, such as a free radical. Examples of such groups include, but are not limited to, benzophenones, azides, and the like.

As used herein, the term "pharmaceutically acceptable salt" includes those derived from pharmaceutically acceptable bases and is non-toxic. Examples of suitable bases include choline, ethanolamine and ethylenediamine. Na^+, K^+, and Ca^{++} salts are also contemplated to be within the scope of the invention (also see Pharmaceutical salts, Birge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19, incorporated herein by reference).

Preferred embodiments

Core:

Preferably, compounds of the present invention have the following formula (II):

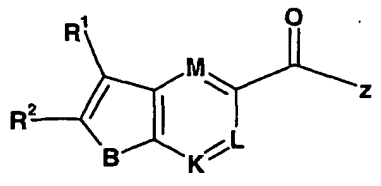


(II)

wherein, preferably, **A** is O, S, or NR^1.

More preferably, **A** is NR^1.

Preferably, compounds of the present invention have the following formula (III):



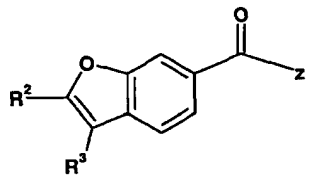
(III)

wherein, preferably, **B** is NR^3.

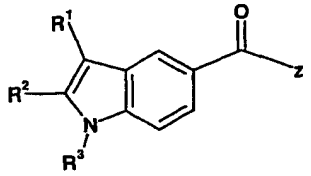
With respect to compounds of formula (II) and (III), preferably, **M**, **K** and **L** is CH or

N. More preferably, **M**, **K** and **L** is CH.

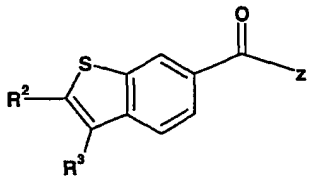
More preferably, compounds of the present invention have the following formulae:



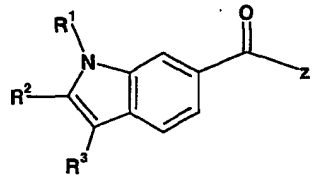
IIa



IIIa

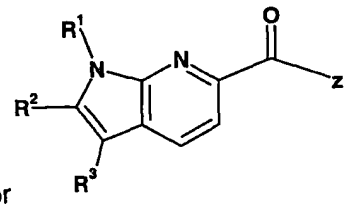


IIb



IIc

or



IId

R^1:

Preferably R^1 is selected from the group consisting of: H or (C_{1-6})alkyl. More preferably, R^1 is H, CH_3, isopropyl, or isobutyl. Even more preferably, R^1 is H or CH_3. Most preferably, R^1 is CH_3.

R^2:

Preferably, R^2 is $CON(R^{22})_2$, wherein each R^{22} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**, or both R^{22} are bonded together to form a 5, 6 or 7-membered saturated heterocycle with the nitrogen to which they are attached;

or R^2 is selected from: H, halogen, (C_{1-6})alkyl, haloalkyl, (C_{2-6})alkenyl, (C_{5-7})cycloalkenyl, 6 or 10-membered aryl or **Het**; wherein each of said alkyl, haloalkyl, (C_{2-6})alkenyl, (C_{5-7})cycloalkenyl, aryl or **Het** is optionally substituted with R^{20}, wherein

R^{20} is defined as:

- 1 to 4 substituents selected from: halogen, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, $(C_{3-}$

$_{7}$)cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;

said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het**, (C1-6alkyl)aryl or (C1-6alkyl)**Het**, all of which being optionally substituted with R^{150}, wherein R^{150} is preferably:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl) or (C_{3-7})cycloalkyl, said alkyl or cycloalkyl optionally substituted with R^{160};

d) SR^{108}, SO_3H, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het** and heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, or (C_{3-7})cycloalkyl, and R^{112} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, and heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl and cycloalkyl being optionally substituted with R^{160}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl) or (C_{3-7})cycloalkyl, or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl

and cycloalkyl being optionally substituted with R^{160};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

More preferably, R^2 is selected from: aryl or **Het**, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloalkyl, N_3, or

a) (C_{1-6})alkyl optionally substituted with OH, $O(C_{1-6})$alkyl or $SO_2(C_{1-6}$ alkyl);

b) (C_{1-6})alkoxy;

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{112} is 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle, each of said alkyl, cycloalkyl, aryl, **Het**, alkyl-aryl or alkyl-**Het**; being optionally substituted with halogen or:

- OR^{2h} or $N(R^{2h})_2$, wherein each R^{2h} is independently H, (C_{1-6})alkyl, or both R^{2h} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle;

f) $NHCOR^{117}$ wherein R^{117} is (C_{1-6})alkyl, $O(C_{1-6})$alkyl or $O(C_{3-7})$cycloalkyl;

i) CO-aryl; and

k) $CONH_2$, $CONH(C_{1-6}alkyl)$, $CON(C_{1-6}alkyl)_2$, CONH-aryl, or $CONHC_{1-6}$alkyl aryl.

Still, more preferably, R^2 is aryl or **Het**, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloalkyl, or

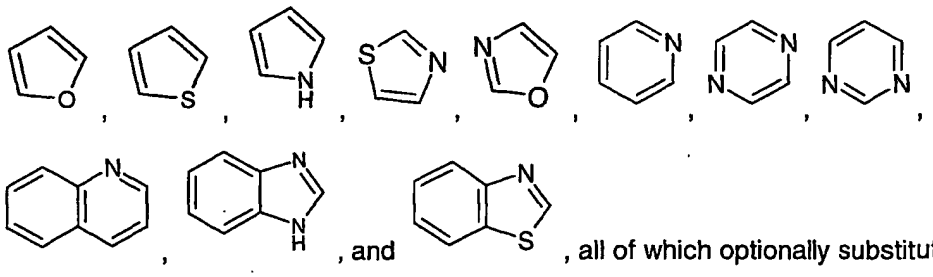
a) (C_{1-6})alkyl optionally substituted with OH, $O(C_{1-6})$alkyl or $SO_2(C_{1-6}alkyl)$;

b) (C_{1-6})alkoxy; and

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{112} is 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl or (C_{1-6})alkyl-**Het**; or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle, each of said alkyl, cycloalkyl, aryl, **Het**, alkyl-aryl or alkyl-**Het**; or being optionally substituted with halogen or:

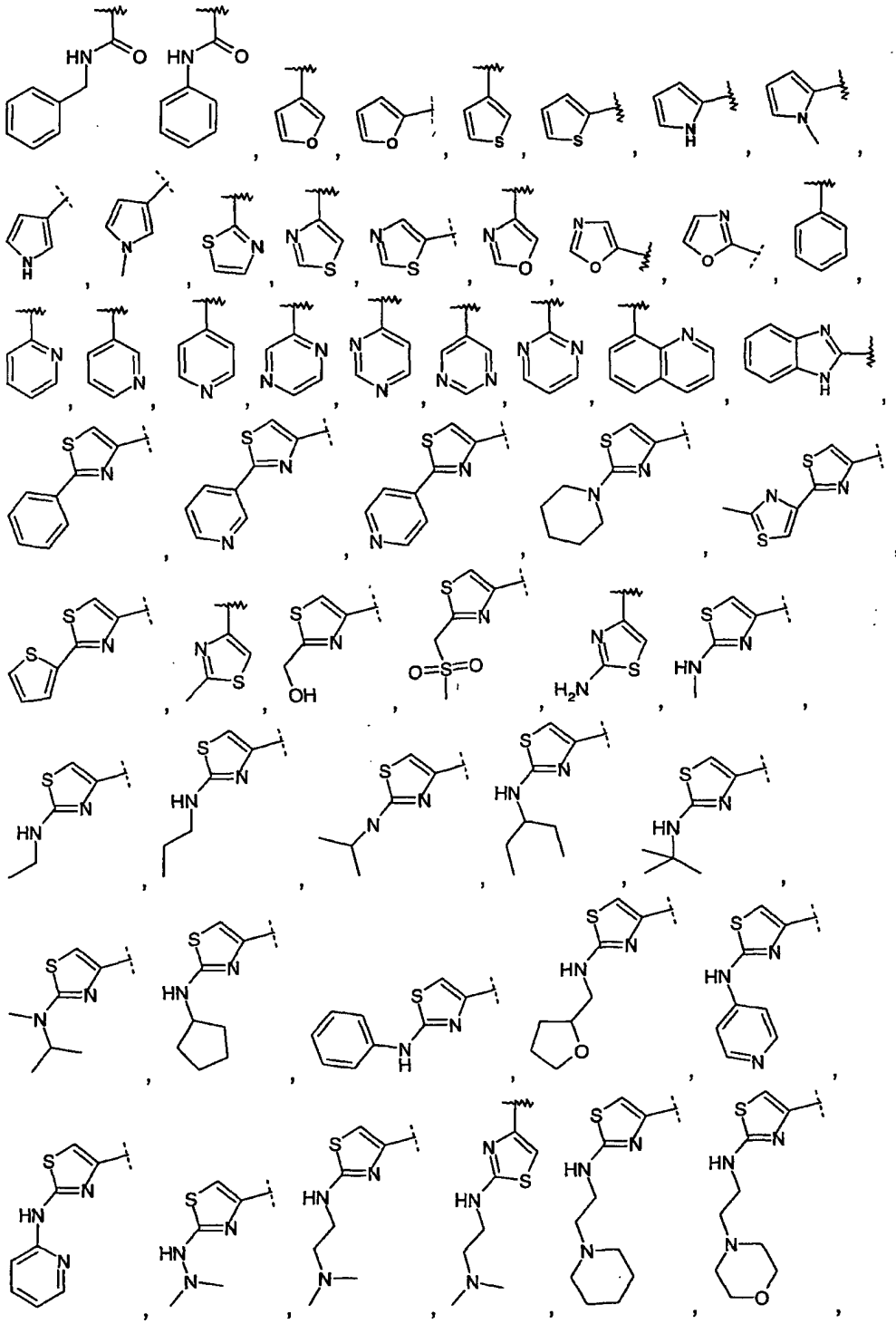
- OR^{2h} or $N(R^{2h})_2$, wherein each R^{2h} is independently H, (C_{1-6})alkyl, or both R^{2h} are covalently bonded together and to the nitrogen to which they are attached to form a nitrogen-containing heterocycle.

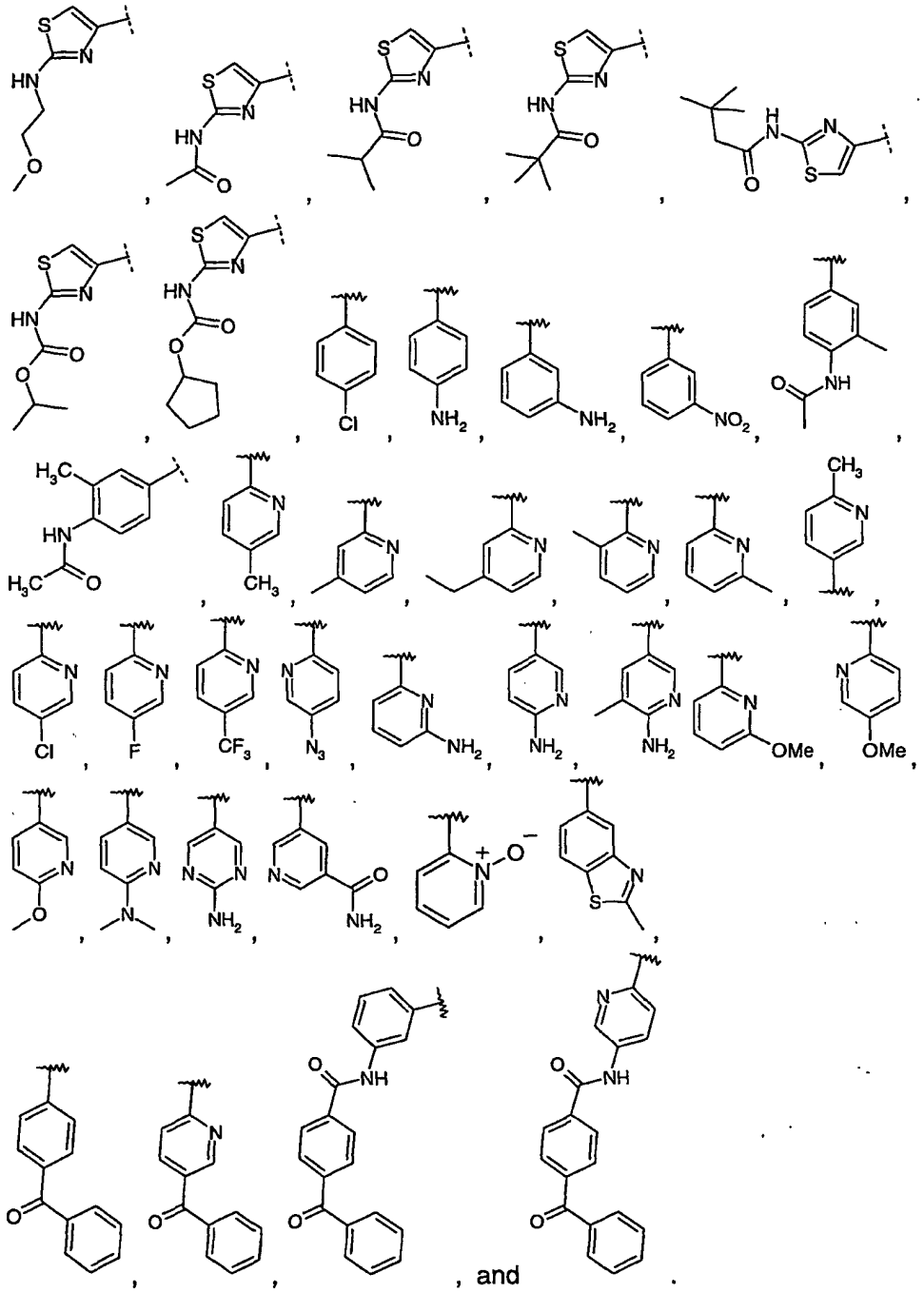
Even more preferably, R^2 is phenyl or a heterocycle selected from:



, all of which optionally substituted as defined above.

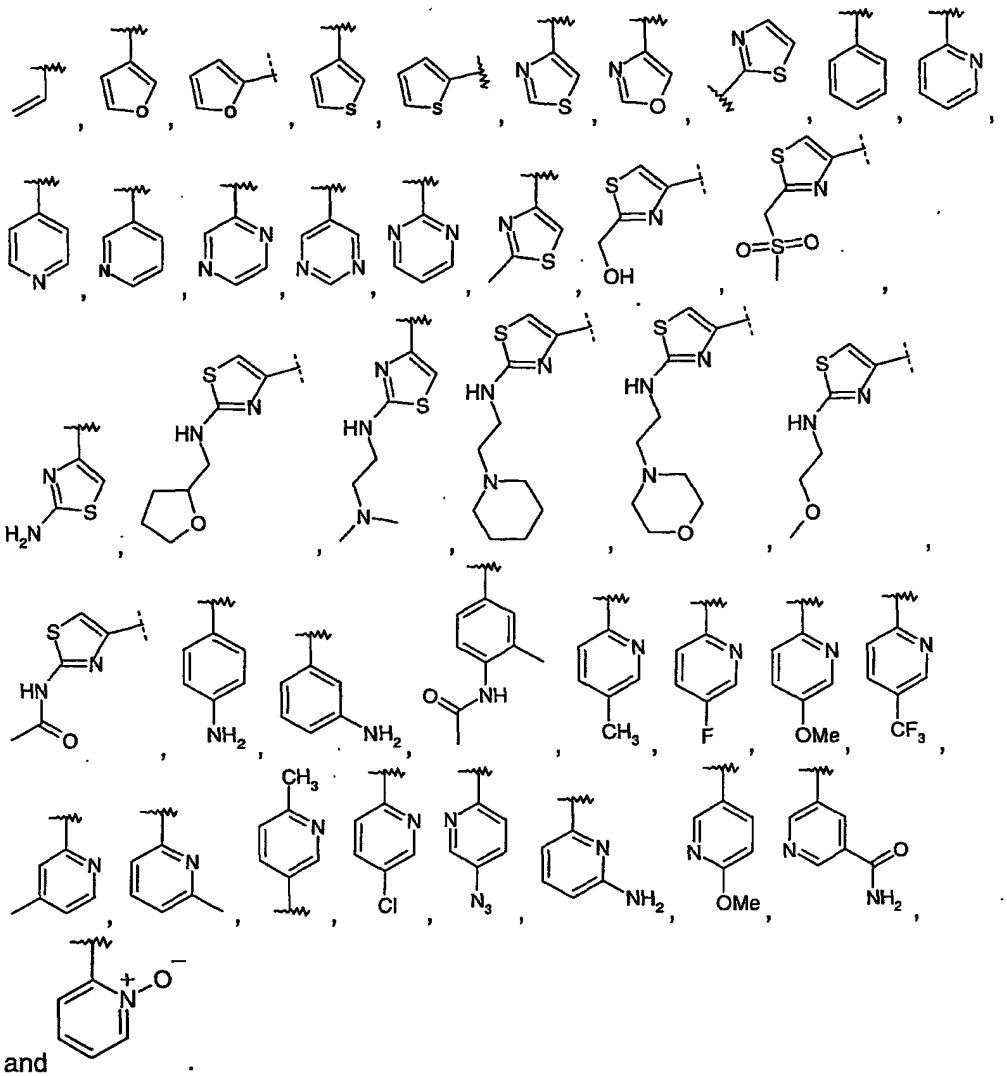
Even more preferably, R^2 is selected from the group consisting of:
H, Br, $CONHCH_3$, $CON(CH_3)_2$, $CONH_2$, $CH=CH_2$,





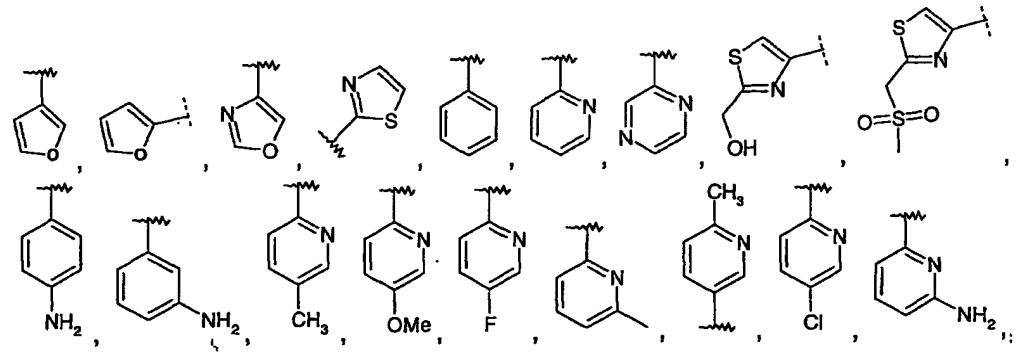
and

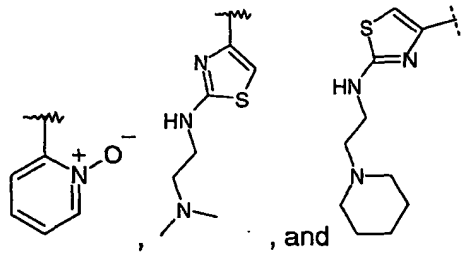
Still more preferably, R^2 is selected from:



and

Most preferably, R^2 is selected from:





, and .

R^3:

Preferably, R^3 is selected from (C_{3-7})cycloalkyl, (C_{3-7})cycloalkenyl, (C_{6-10})bicycloalkyl, (C_{6-10})bicycloalkenyl, 6- or 10-membered aryl, or **Het**. More preferably, R^3 is (C_{3-7})cycloalkyl. Most preferably, R^3 is cyclopentyl, or cyclohexyl.

Y:

Preferably Y^1 is O.

Z:

Preferably, **Z** is OR^6 wherein R^6 is $(C_{1-6}$alkyl)aryl substituted with:

- 1 to 4 substituents selected from:

a) (C_{1-6})alkyl substituted with R^{150a}, haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, said haloalkyl, cycloalkyl, spirocycloalkyl, alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with R^{150}, wherein R^{150a} is the same as R^{150} but is not $COOR^{150b}$, $N(R^{150b})_2$, $NR^{150b}C(O)R^{150b}$, OR^{150b}, SR^{150b}, SO_2R^{150b}, $SO_2N(R^{150b})_2$, wherein R^{150b} is H or unsubstituted C_{1-6}alkyl;

b) OR^{104} wherein R^{104} is $(C_{1-6}$alkyl) substituted with R^{150}, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108a}, $SO_2N(R^{108a})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with

R^{150}, wherein R^{108a} is the same as R^{108} but is not H or unsubstituted C_{1-6}alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl, or R^{112} is also $COOR^{115}$ or SO_2R^{115a} wherein R^{115} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{115a} is the same as R^{115} but is not H or unsubstituted alkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each (C_{1-6})alkyl substituted with R^{150}, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or C_{1-6}alkyl and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{124} is OH or $O(C_{1-6}$alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is (C_{1-6})alkyl substituted with R^{150}, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl and $(C_{1-}$

$_6$alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, provided that when R^{129} is H or unsubstituted alkyl, R^{130} is not H or unsubstituted alkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150}; wherein R^{150} is:

- 1 to 3 substituents selected from: halogen or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are

attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and

heterocycle being optionally substituted with R^{150};

wherein, R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above.

More preferably, **Z** is OR^6 wherein R^6 is (C_{1-6}alkyl)aryl substituted with:

- 1 to 4 substituents selected from:

a) (C_{1-6})alkyl substituted with R^{150a}, haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, said haloalkyl, cycloalkyl, spirocycloalkyl, alkenyl, alkynyl and alkyl-cycloalkyl being optionally substituted with R^{150}, wherein R^{150a} is the same as R^{150} but is not $COOR^{150b}$, $N(R^{150b})_2$, $NR^{150b}C(O)R^{150b}$, OR^{150b}, SR^{150b}, SO_2R^{150b}, $SO_2N(R^{150b})_2$, wherein R^{150b} is H or unsubstituted C_{1-6}alkyl;

b) OR^{104} wherein R^{104} is (C_{1-6}alkyl) substituted with R^{150}, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SO_3H, $SO_2N(R^{108a})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl and aryl, said alkyl and aryl being optionally substituted with R^{150}, wherein R^{108a} is the same as R^{108} but is not H or unsubstituted C_{1-6}alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, (C_{1-6})alkyl, provided that when R^{111} is H or unsubstituted alkyl, R^{112} is not H or unsubstituted alkyl, or R^{112} is also $COOR^{115}$ or SO_2R^{115a} wherein R^{115} is H, (C_{1-6})alkyl or (C_{1-6}alkyl)aryl, and R^{115a} is C_{1-6}alkyl substituted with R^{150} or (C_{1-6}alkyl)aryl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each (C_{1-6})alkyl substituted with R^{150}, (C_{3-7})cycloalkyl, aryl, **Het**, said (C_{3-7})cycloalkyl, aryl, **Het** being optionally

substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, aryl, **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or C_{1-6}alkyl and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), aryl or **Het**, or R^{124} is OH or $O(C_{1-6}$alkyl), said alkyl, aryl and **Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is (C_{1-6})alkyl substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, aryl or **Het**, provided that when R^{129} is H or unsubstituted alkyl, R^{130} is not H or unsubstituted alkyl, said alkyl, aryl and **Het** being optionally substituted with R^{150};

l) aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, all of which being optionally substituted with R^{150}; wherein R^{150} is:

- 1 to 3 substituents selected from: halogen or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{2-6})alkenyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, aryl or **Het**, and R^{112} is H, (C_{1-6})alkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, said alkyl, aryl or **Het** being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), aryl or **Het**, or R^{124} is OH or $O(C_{1-6}$alkyl), said alkyl, aryl and **Het** being

optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

wherein, R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and R^{162} are as defined above.

Even more preferably, **Z** is OR^6 wherein R^6 is (C_{2-6})alkenyl, (C_{1-6})alkyl-**Het**, wherein said alkenyl or alkyl-**Het**, is optionally substituted with R^{60}, wherein preferably R^{60} is:

- 1 to 4 substituents selected from: halogen; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-}$

$_6$alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{150}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated

heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150}, wherein R^{150} is defined as:

- 1 to 3 substituents selected from: halogen or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted

with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or (C_{1-6})alkyl optionally substituted with R^{160}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SR^{161}, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H,

(C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

Even more preferably, R^{60} is:

- 1 to 4 substituents selected from: halogen; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SO_3H, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl or aryl, said alkyl and aryl being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, (C_{1-6})alkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl or $(C_{1-6}$alkyl)aryl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl or **Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl or **Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or (C_{1-6})alkyl, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), aryl or **Het**, or R^{124} is OH or $O(C_{1-6}$alkyl), said alkyl, aryl and **Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H or (C_{1-6})alkyl optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, aryl or **Het,** said alkyl, aryl and **Het** being optionally substituted with R^{150};

l) aryl, **Het,** $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het,** all of which being optionally substituted with R^{150}, wherein R^{150} is defined as:

- 1 to 3 substituents selected from: halogen; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{2-6})alkenyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, aryl or **Het**, and R^{112} is H, (C_{1-6})alkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl or aryl, said alkyl, aryl and **Het** being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, aryl or **Het**, said alkyl, aryl and **Het** being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or (C_{1-6})alkyl optionally substituted with R^{160}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), aryl or **Het**, or R^{124} is OH or $O(C_{1-6}$alkyl), said alkyl, aryl and **Het** being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H or (C_{1-6})alkyl optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, aryl or **Het,** said alkyl, aryl and **Het** being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H,

SR^{161}, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

Most preferably, **Z** is $N(R^{6a})R^6$ wherein R^{6a} is H or C_{1-6}alkyl. More preferably, R^{6a} is H.

Preferably, R^6 is (C_{2-6})alkenyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkenyl, aryl, **Het**, alkyl-aryl or alkyl-**Het**, are all optionally substituted with:

- 1 to 4 substituents selected from: halogen, OPO_3H, NO_2, cyano, azido, $C(=NH)NH_2$, $C(=NH)NH(C_{1-6})$alkyl or $C(=NH)NHCO(C_{1-6})$alkyl; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2NH(C_{1-6}$alkyl) or $SO_2NHC(O)C_{1-6}$alkyl;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or

(C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150}, wherein, preferably, R^{150} is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{119} and R^{120} are covalently bonded

together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H or (C_{1-6})alkyl optionally substituted with R^{160}; and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

More preferably, R^6 is (C_{2-6})alkenyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein

said alkenyl, aryl, **Het**, alkyl-aryl, or alkyl-**Het**, are all optionally substituted with:

- 1 to 4 substituents selected from: halogen, NO_2, cyano, azido; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SH, S(C_{1-6}alkyl), SO_3H, $SO_2NH(C_{1-6}alkyl)$ or $SO_2NHC(O)C_{1-6}alkyl$;

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het**, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, said alkyl, cycloalkyl being optionally substituted with R^{150}, or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl) or (C_{3-7})cycloalkyl, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-}

$_7$)cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

l) aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150}, wherein, preferably, R^{150} is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

d) SH, S(C_{1-6}alkyl), SO_3H, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}; and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or R^{124} is OH or $O(C_{1-6}$alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein, preferably, R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl,

$COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H or (C_{1-6})alkyl.

Most preferably, R^6 is C_{2-6}alkenyl, phenyl, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkenyl, phenyl and the alkyl portion of said alkyl-aryl, or alkyl-**Het**, are optionally substituted with 1 to 3 of:

a) (C_{1-6}) alkyl C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, all of which optionally substituted with C_{1-6}alkyl or C_{1-6}alkoxy;

NH_2, NH(Me) or $N(Me)_2$

e) NHR^{112} wherein R^{112} is aryl, **Het**, $(C_{1-6}$alkyl)aryl, $(C_{1-6}$alkyl)**Het**, said aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, being optionally substituted with R^{150};

j) COOH;

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl, and $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

l) phenyl or **Het**, both optionally substituted with R^{150}, wherein, preferably, R^{150} is selected from:

- 1 or 2 substituents selected from: halogen, NO_2, cyano or azido;
- 1 or 2 substituents selected from:

a) (C_{1-6}) alkyl or (C_{2-6})alkenyl, both optionally substituted with COOH or $CONH_2$;

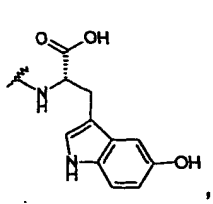
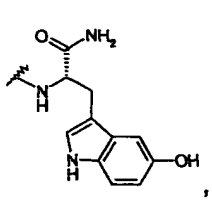
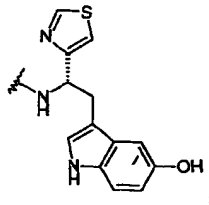
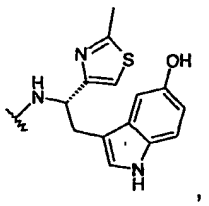
b) OR^{104} wherein R^{104} is H or $(C_{1-6}$alkyl) optionally substituted with COOH;

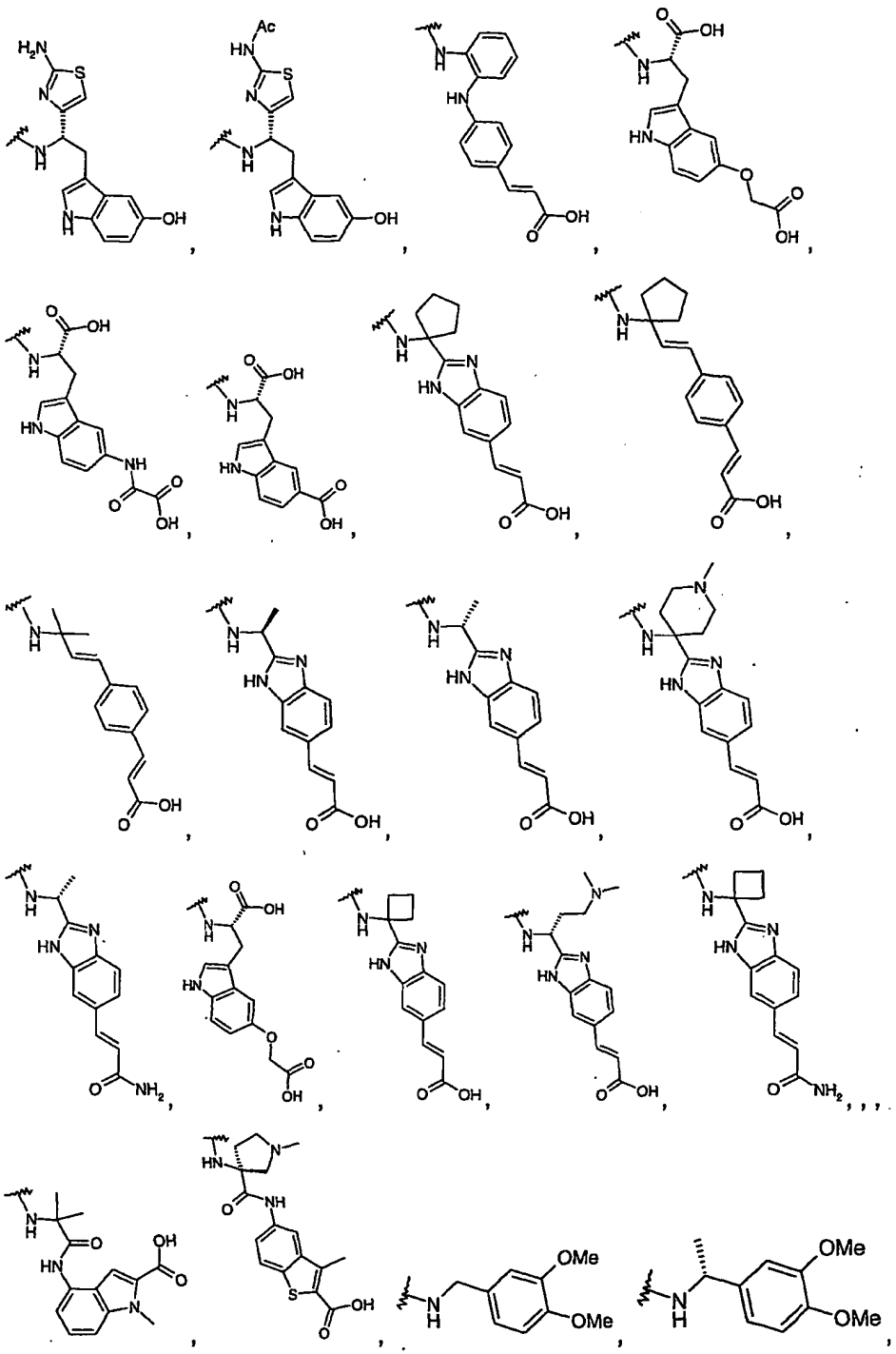
h) NHCOCOOH;

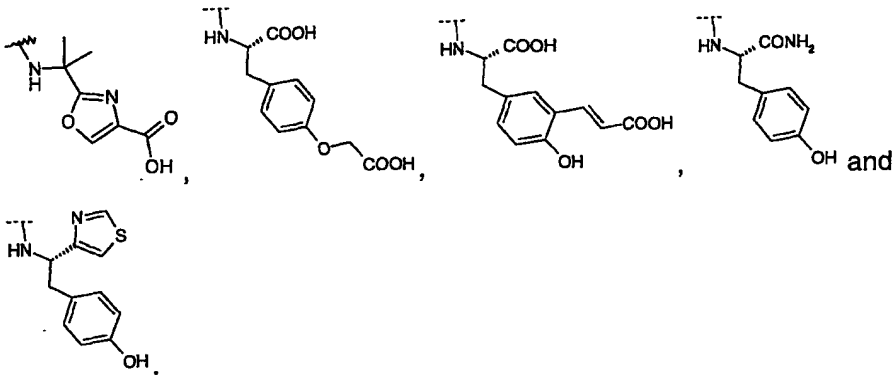
j) COOH; and

k) $CONH_2$.

Preferably, **Z** is

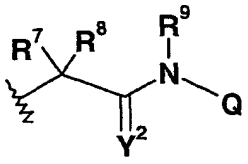









Diamides:

Most preferably, R^6 is:



wherein, preferably, R^7 and R^8 are each independently H, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, wherein said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het** are optionally substituted with R^{70}; or

R^7 and R^8 are covalently bonded together to form second (C_{3-7})cycloalkyl or a 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S; or when **Z** is $N(R^{6a})R^6$, either of R^7 or R^8 is covalently bonded to R^{6a} to form a nitrogen-containing 5-or 6-membered heterocycle; wherein, preferably, R^{70} is selected from:

- 1 to 4 substituents selected from: halogen, NO_2, cyano, azido; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, $(C_{1-6}$alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is

independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded

together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

i) COR^{127} wherein R^{127} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150}, wherein, preferably, R^{150} is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano, azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-6})alkynyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl) or (C_{3-7})cycloalkyl, said alkyl and cycloalkyl being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ wherein R^{108} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl or cycloalkyl being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, and R^{112} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het**, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl,

cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said (C_{1-6})alkyl or (C_{3-7})cycloalkyl being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said alkyl or cycloalkyl being optionally substituted with R^{160};
or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl) or (C_{3-7})cycloalkyl, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, OR^{161}, $N(R^{162})_2$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H or (C_{1-6})alkyl.

More preferably, R^7 and R^8 are each independently H, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, all of which optionally substituted with from 1 to 4 substituents selected from halogen or:

a) (C_{1-6})alkyl; and

b) $N(R^{8a'})_2$, COR^{8a}, or $SO_2R^{8a''}$ $COOR^{8a}$, $COCOOR^{8a}$, $CON(R^{8a'})_2$, $COCON(R^{8a'})_2$, wherein each R^{8a} or $R^{8a'}$ are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or each $R^{8a'}$ are independently covalently bonded together and to the nitrogen to which they are both bonded to form a 5, 6 or 7-membered saturated heterocycle; or $R^{8a''}$ is independently (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl.

or R^7 and R^8 are covalently bonded together to form (C_{3-7})cycloalkyl, 4, 5- or 6-membered heterocycle having from 1 to 3 heteroatom selected from O, N, and S.

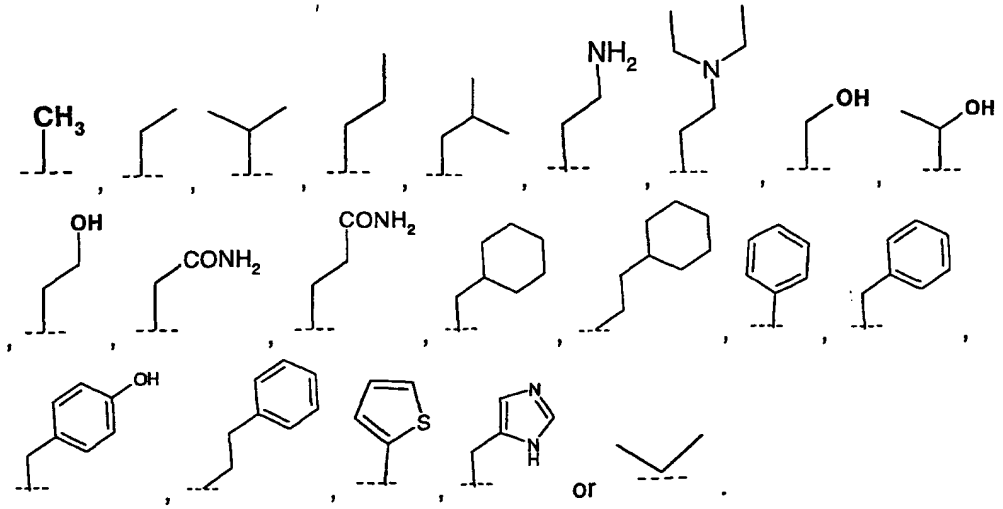
Most preferably, R^7 and R^8 are each independently H, (C_{1-6})alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**; or R^7 and R^8 are covalently bonded together to form cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidine, piperidine, tetrahydrofuran, tetrahydropyran, or pentamethylene sulfide;

wherein said alkyl, haloalkyl, (C_{3-7})cycloalkyl, 6- or 10-membered aryl, **Het**, (C_{1-6})alkyl-aryl, (C_{1-6})alkyl-**Het**, cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidine, piperidine, tetrahydrofuran, tetrahydropyran, or pentamethylene sulfide are optionally monosubstituted with substituents selected from:

a) (C_{1-6})alkyl; and

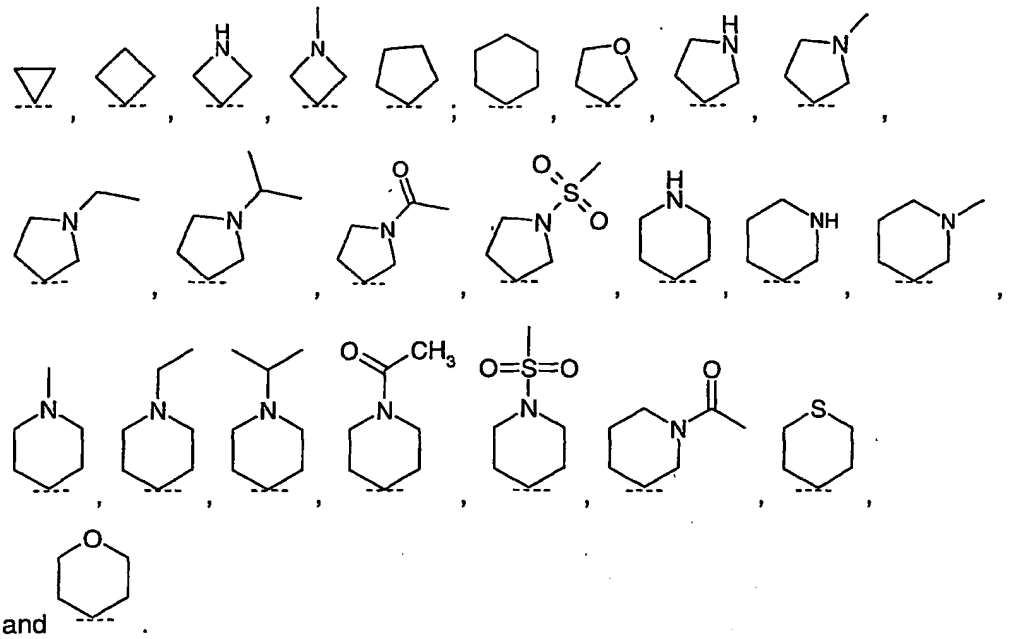
c) NH_2, $N(CH_2CH)_2$, $COCH_3$, or SO_2CH_3.

Even more preferably, R^7 and R^8 are selected from:



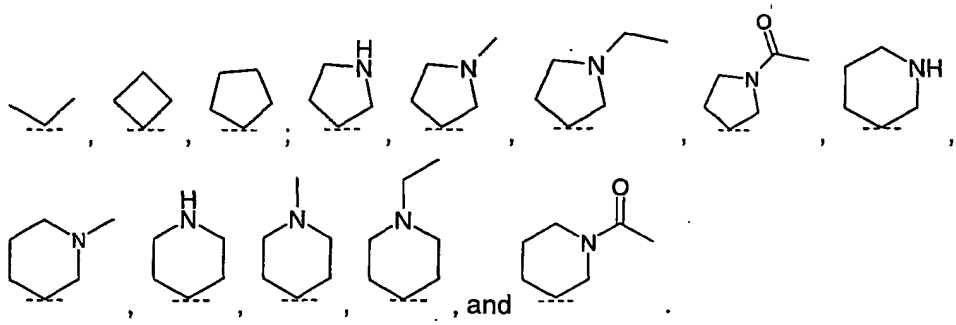
or .

R^7 and R^8 together form:



and .

Most preferably, R^7 and R^8 are selected from the group consisting of:



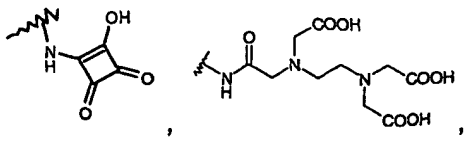
, and .

R^9:

Preferably R^9 is H; or R^9 is covalently bonded to either of R^7 or R^8 to form a 5- or 6-membered heterocycle. More preferably, R^9 is H.

Q:

Preferably, **Q** is a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)-Het, all of which being optionally substituted with:



, or R^{100};

wherein R^{100} is:

- 1 to 4 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108} wherein R^{108} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} and R^{122} is each H, (C_{1-6})alkyl, (C_{3-}

$_7$)cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, all of which being optionally substituted with R^{150};

wherein R^{150} is selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, C_{3-7} spirocycloalkyl optionally containing 1 or 2 heteroatom, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are

covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{118} is covalently bonded to R^{119} and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-

cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SR^{161}, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

More preferably, **Q** is a 6- or 10-membered aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)-Het, all of which being optionally substituted with:

- 1 to 4 substituents selected from: halogen,NO_2, cyano or azido; or
- 1 to 4 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is

independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, and R^{112} is H, CN, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** , $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted with R^{150};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** or heterocycle being optionally substituted with R^{150};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{150}, and R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** or R^{124} is OH or O(C_{1-6}alkyl) or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-}

$_7$)cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het,** said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or(C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl and (C_{1-6}alkyl)**Het** being optionally substituted with R^{150};

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, **Het,** (C_{1-6}alkyl)aryl, (C_{1-6}alkyl)**Het** and heterocycle being optionally substituted with R^{150};

l) aryl, **Het,** (C1-6alkyl)aryl or (C1-6alkyl)**Het**, all of which being optionally substituted with R^{150}, wherein R^{150} is preferably selected from:

- 1 to 3 substituents selected from: halogen, NO_2, cyano or azido; or
- 1 to 3 substituents selected from:

a) (C_{1-6}) alkyl or haloalkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which optionally substituted with R^{160};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl), (C_{3-7})cycloalkyl, or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, said alkyl, cycloalkyl, aryl and **Het** being optionally substituted with R^{160};

c) $OCOR^{105}$ wherein R^{105} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{160};

d) SR^{108}, $SO_2N(R^{108})_2$ or $SO_2N(R^{108})C(O)R^{108}$ wherein each R^{108} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or both R^{108} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl or heterocycle being optionally substituted with R^{160};

e) $NR^{111}R^{112}$ wherein R^{111} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, and R^{112} is H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl, $COOR^{115}$ or SO_2R^{115} wherein R^{115} is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or both R^{111} and R^{112} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl, aryl, **Het**, (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, or heterocycle being optionally substituted

with R^{160};

f) $NR^{116}COR^{117}$ wherein R^{116} and R^{117} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het**, said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl, **Het**, $(C_{1-6}$alkyl)aryl or $(C_{1-6}$alkyl)**Het** being optionally substituted with R^{160};

g) $NR^{118}CONR^{119}R^{120}$, wherein R^{118}, R^{119} and R^{120} is each H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, or R^{119} and R^{120} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle; said alkyl, cycloalkyl or heterocycle being optionally substituted with R^{160};

h) $NR^{121}COCOR^{122}$ wherein R^{121} is H, (C_{1-6})alkyl optionally substituted with R^{160}; or R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H, $(C_{1-6}$alkyl) or (C_{3-7})cycloalkyl, or R^{124} is OH or $O(C_{1-6}$alkyl), or both R^{124} are covalently bonded together to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

j) tetrazole, $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, said (C_{1-6})alkyl and (C_{3-7})cycloalkyl being optionally substituted with R^{160}; and

k) $CONR^{129}R^{130}$ wherein R^{129} and R^{130} are independently H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl, or both R^{129} and R^{130} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle, said alkyl, cycloalkyl and heterocycle being optionally substituted with R^{160};

wherein R^{160} is defined as 1 or 2 substituents selected from: tetrazole, halogen, CN, C_{1-6}alkyl, haloalkyl, $COOR^{161}$, SO_3H, SO_2R^{161}, OR^{161}, $N(R^{162})_2$, $SO_2N(R^{162})_2$, $NR^{162}COR^{162}$ or $CON(R^{162})_2$, wherein R^{161} and each R^{162} is independently H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-6})alkyl-(C_{3-7})cycloalkyl; or both R^{162} are covalently bonded together and to the nitrogen to which they are attached to form a 5, 6 or 7-membered saturated heterocycle.

Most preferably, **Q** is a 6- or 10-membered aryl or **Het**, both being optionally substituted with:

- 1 to 3 halogen, NO_2, cyano, azido; or
- 1 to 3 substituents selected from:

a) first (C_{1-6}) alkyl or haloalkyl, first (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which are optionally substituted with R^{150};

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl);

d) SO_2NHR^{108} wherein R^{108} is H or (C_{1-6})alkyl;

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H or (C_{1-6})alkyl;

f) $NHCOR^{117}$ wherein R^{116} is H or (C_{1-6})alkyl;

g) $NHCONR^{119}R^{120}$, wherein R^{119} and R^{120} is each independently H or (C_{1-6})alkyl;

h) $NHCOCOR^{122}$ wherein R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H or (C_{1-6}alkyl);

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl;

k) $CONHR^{130}$ wherein R^{130} is H, (C_{1-6})alkyl;

l) 6- or 10-membered aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het**, said aryl, **Het,** (C_{1-6}alkyl)aryl or (C_{1-6}alkyl)**Het** being optionally substituted with R^{150}; and

wherein, preferably, R^{150} is selected from:

- 1 to 3 halogens; or
- 1 to 3 substituents selected from:

a) first (C_{1-6}) alkyl or haloalkyl, first (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{2-8})alkynyl, (C_{1-6}) alkyl-(C_{3-7})cycloalkyl, all of which are optionally substituted with tetrazole, OR^{102}, $COOR^{102}$, wherein R^{102} is H or (C_{1-6})alkyl;

b) OR^{104} wherein R^{104} is H, (C_{1-6}alkyl);

d) SO_2NHR^{108} wherein R^{108} is H or (C_{1-6})alkyl;

e) $NR^{111}R^{112}$ wherein both R^{111} and R^{112} are independently H or (C_{1-6})alkyl;

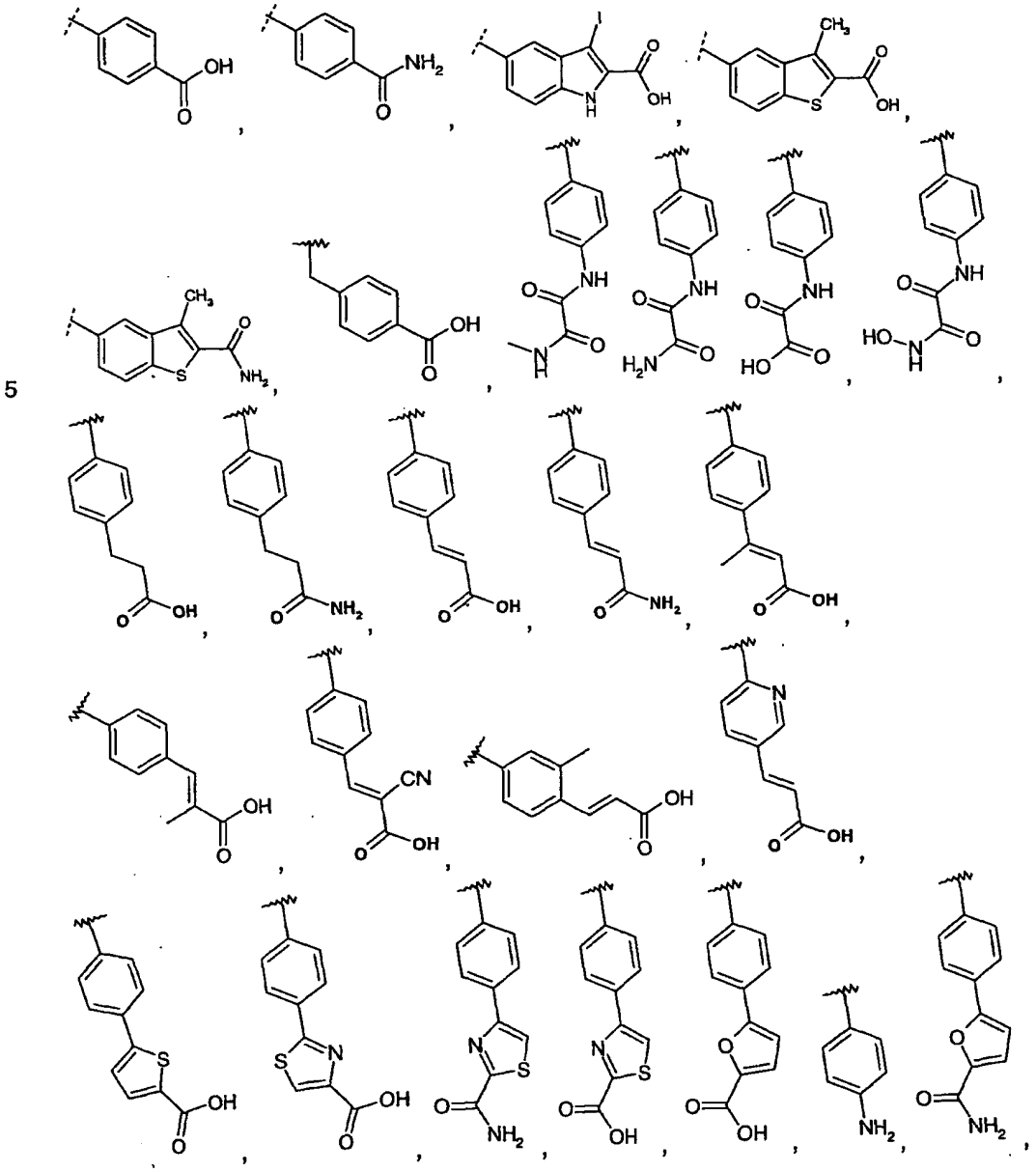
f) $NHCOR^{117}$ wherein R^{116} is H or (C_{1-6})alkyl; and

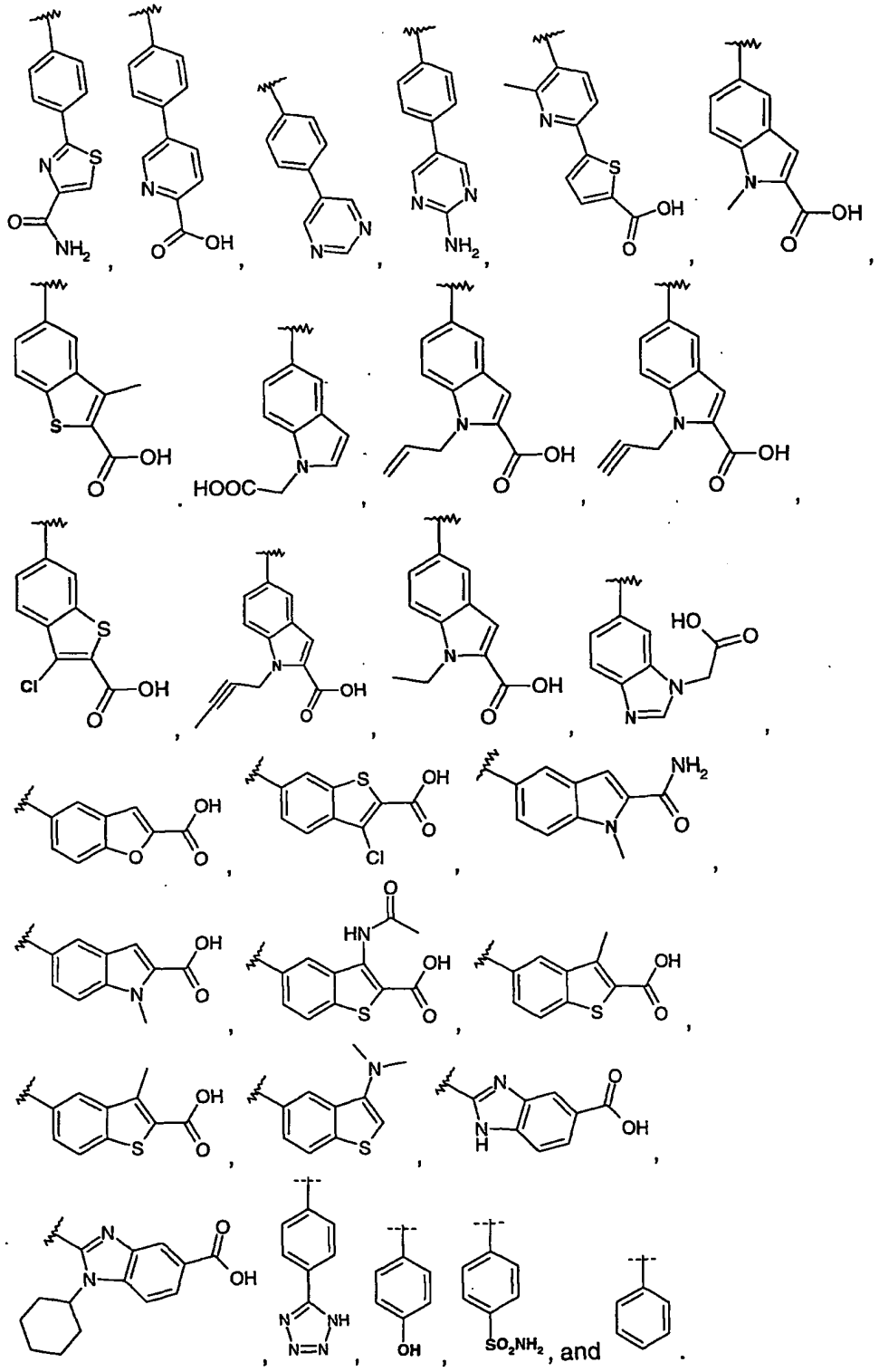
h) $NHCOCOR^{122}$ wherein R^{122} is OR^{123} or $N(R^{124})_2$ wherein R^{123} and each R^{124} is independently H or (C_{1-6}alkyl);

j) $COOR^{128}$ wherein R^{128} is H, (C_{1-6})alkyl; and

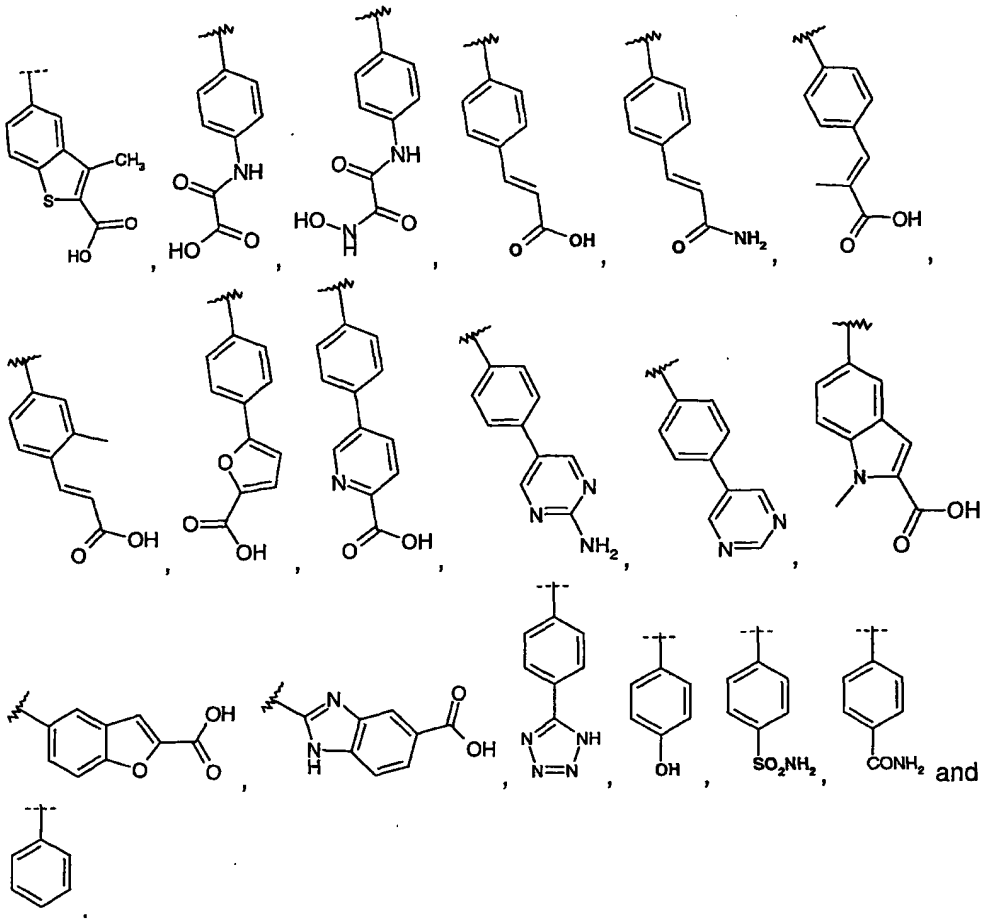
k) $CONHR^{130}$ wherein R^{130} is H, (C_{1-6})alkyl.

More preferably **Q** is selected from:





Most preferably, **Q** is selected from:



and

Specific embodiments

Included within the scope of this invention are all compounds of formula I as presented in Tables 1 to 9.

Polymerase activity

The ability of the compounds of formula (I) to inhibit RNA synthesis by the RNA dependent RNA polymerase of HCV can be demonstrated by any assay capable of measuring RNA dependent RNA polymerase activity. A suitable assay is described in the examples.

Specificity for RNA dependent RNA polymerase activity

To demonstrate that the compounds of the invention act by specific inhibition of HCV polymerase, the compounds may be tested for inhibitory activity in a DNA dependent RNA polymerase assay.

When a compound of formula (I), or one of its therapeutically acceptable salts, is employed as an antiviral agent, it is administered orally, topically or systemically to mammals, e.g. humans, rabbits or mice, in a vehicle comprising one or more pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice.

For oral administration, the compound or a therapeutically acceptable salt thereof can be formulated in unit dosage forms such as capsules or tablets each containing a predetermined amount of the active ingredient, ranging from about 25 to 500 mg, in a pharmaceutically acceptable carrier.

For topical administration, the compound can be formulated in pharmaceutically accepted vehicles containing 0.1 to 5 percent, preferably 0.5 to 5 percent, of the active agent. Such formulations can be in the form of a solution, cream or lotion.

For parenteral administration, the compound of formula (I) is administered by either intravenous, subcutaneous or intramuscular injection, in compositions with pharmaceutically acceptable vehicles or carriers. For administration by injection, it is preferred to use the compounds in solution in a sterile aqueous vehicle which may also contain other solutes such as buffers or preservatives as well as sufficient quantities of pharmaceutically acceptable salts or of glucose to make the solution isotonic.

Suitable vehicles or carriers for the above noted formulations are described in pharmaceutical texts, e.g. in "Remington's The Science and Practice of Pharmacy", 19th ed., Mack Publishing Company, Easton, Penn., 1995, or in "Pharmaceutical Dosage Forms And Drugs Delivery Systems", 6th ed., H.C. Ansel et al., Eds., Williams & Wilkins, Baltimore, Maryland, 1995.

The dosage of the compound will vary with the form of administration and the particular active agent chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small increments until the optimum effect under the circumstance is reached. In general, the compound of formula I is

most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

For oral administration, the compound or a therapeutically acceptable salt is administered in the range of 10 to 200 mg per kilogram of body weight per day, with a preferred range of 25 to 150 mg per kilogram.

For systemic administration, the compound of formula (I) is administered at a dosage of 10 mg to 150 mg per kilogram of body weight per day, although the aforementioned variations will occur. A dosage level that is in the range of from about 10 mg to 100 mg per kilogram of body weight per day is most desirably employed in order to achieve effective results.

When the compositions of this invention comprise a combination of a compound of formula I and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

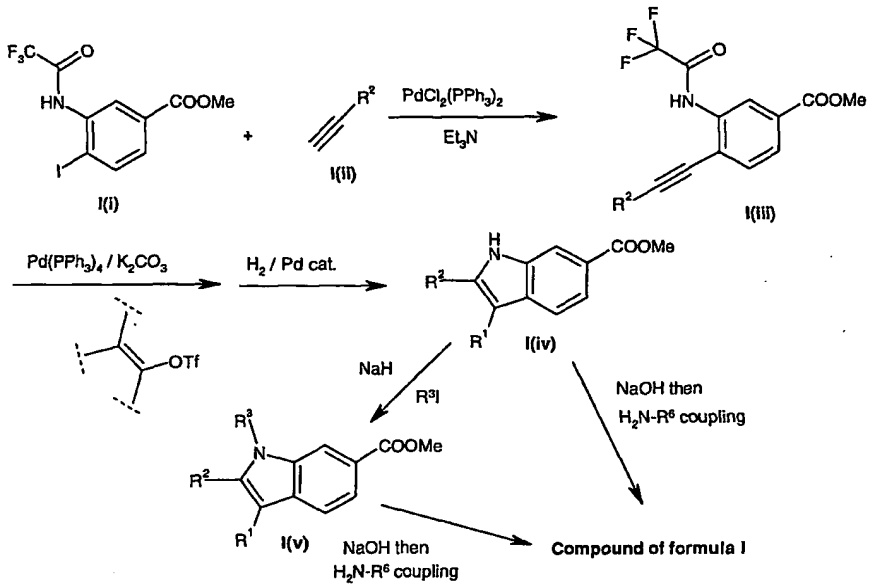
When these compounds or their pharmaceutically acceptable salts are formulated together with a pharmaceutically acceptable carrier, the resulting composition may be administered *in vivo* to mammals, such as man, to inhibit HCV polymerase or to treat or prevent HCV virus infection. Such treatment may also be achieved using the compounds of this invention in combination with agents which include, but are not limited to: immunomodulatory agents, such as α-, β-, or γ-interferons; other antiviral agents such as ribavirin, amantadine; other inhibitors of HCV NS5B polymerase; inhibitors of other targets in the HCV life cycle, which include but not limited to, helicase, NS2/3 protease, NS3 protease, or internal ribosome entry site (IRES); or combinations thereof. The additional agents may be combined with the compounds of this invention to create a single dosage form. Alternatively these additional agents may be separately administered to a mammal as part of a multiple dosage form.

Methodology and Synthesis

Indole derivatives or analogs according to the present invention can be prepared from known monocyclic aromatic compounds by adapting known literature sequences such as those described by J.W. Ellingboe et al. (*Tet. Lett.* **1997**, *38*,

7963) and S. Cacchi et al. (*Tet. Lett.* **1992**, *33*, 3915). Scheme 1, shown below wherein R^1, R^2, R^3, R^6, **K**, **L**, and **M** are as described herein illustrate how these procedures can be adapted to the synthesis of compounds of formula **1** of this invention.

Scheme 1



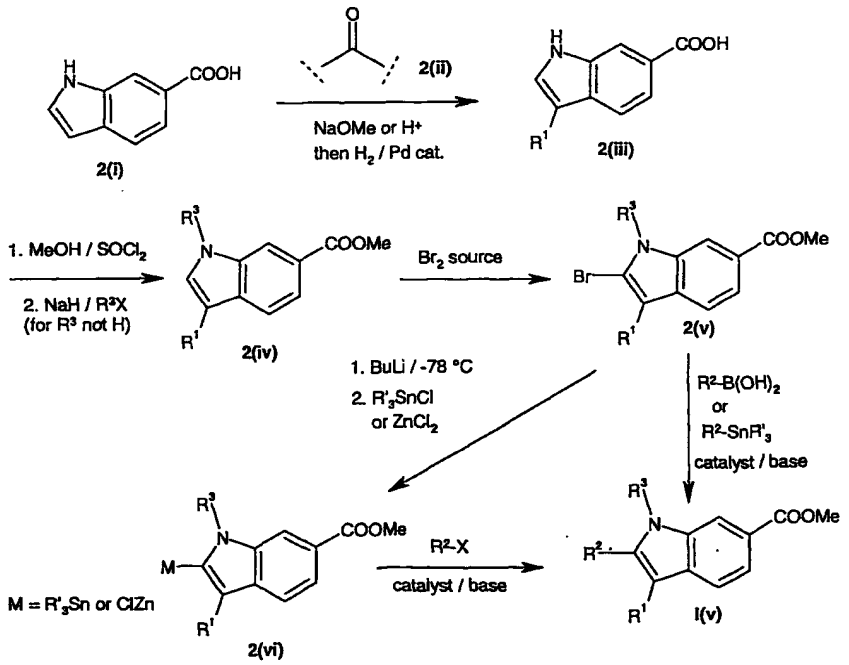
In carrying out the route illustrated in Scheme 1, a suitably protected form of 3-trifluoroacetamido-4-iodobenzoic acid **I(i)** is reacted with an alkyne **I(ii)** in the presence of a metal catalyst (e.g. a palladium metal complex such as $PdCl_2(PPh_3)_2$, Pd_2dba_3, $Pd(PPh_3)_4$ and the like), a base (Et_3N, DIEA and the like or an inorganic basic salt including metal carbonates, fluorides and phosphates), and optionally in the presence of an additional phosphine ligand (triaryl or heteroarylphosphine, dppe, dppf, dppp and the like). Suitable solvents for this reaction include DMF, dioxane, THF, DME, toluene, MeCN, DMA and the like at temperatures ranging from 20 °C to 170 °C, or alternatively without solvent by heating the components together. Alternatively, the cross-coupling reaction can be carried out on a suitably protected form of 3-amino-4-iodobenzoate and the amino group can be trifluoroacetylated in the subsequent step as described by J.W. Ellingboe et al. (*Tet. Lett.* **1997**, *38*, 7963). Reaction of the above diarylalkynes **I(iii)** with an enol triflate under cross-coupling conditions similar to those described above gives after hydrogenation of the douple bond, indole derivatives **I(iv)**. Enol triflates are known and can be prepared from the corresponding ketones by following known literature methods (for example, cyclohexene triflate can be prepared from cyclohexanone, triflic anhydride and a

hindered organic base such as 2,6-di-*tert*-butyl-4-methylpyridine). The hydrogenation of the double bond originally present in R^1 can be carried out with hydrogen gas or a hydrogen donor (ammonium formate, formic acid and the like) in the presence of a metal catalyst (preferably Pd) in a suitable solvent (lower alkyl alcohols, THF etc.).

Finally, following hydrolysis of the ester protecting group in **I(iv),** the resulting 6-carboxyindole derivative **I(v)** is converted to compounds of formula **1** by coupling with the appropriate amine of formula H_2N-R^6. Condensation of the 6-indolecarboxylic acid with amines H_2N-R^6 can be accomplished using standard amide bond forming reagents such as TBTU,HATU, BOP,BroP, EDAC, DCC, isobutyl chloroformate and the like, or by activation of the carboxyl group by conversion to the corresponding acid chloride prior to condensation with an amine. Any remaining protecting group is removed following this step to give compounds of formula **1**.

Alternatively, compounds of formula **1** can be prepared by elaboration from a pre-exisitng indole core by following adaptations of literature procedures as described, for example, by P. Gharagozloo et al. (*Tetrahedron* **1996**, *52*, 10185) or K. Freter (*J. Org. Chem.* **1975**, *40*, 2525). Such a methodology is illustrated in Scheme 2:

Scheme 2



In carrying the route illustrated in Scheme 2, commercially available 6-indolecarboxylic acid **2(i)**, which can also be prepared according to the method of S. Kamiya et al. (*Chem. Pharm. Bull.* **1995**, *43*, 1692) is used as the starting material. The indole **2(i)** is reacted with a ketone **2(ii)** under basic or acidic aldol-type conditions. Suitable conditions to affect this condensation include strong bases such as alkali metal hydroxides, alkoxides and hydrides in solvents such as lower alkyl alcohols (MeOH, EtOH, *tert*BuOH etc.), THF, dioxane, DMF, DMSO, DMA and the like at reaction temperature ranging from –20 °C to 120 °C. Alternatively, the condensation can be carried out under acid conditions using organic or mineral acids or both. Appropriate conditions include mixtures of AcOH and aqueous phosphoric acid at temperatures ranging from 15°C to 120 °C.

Following protection of the carboxylic acid group in the form of an ester (usually lower alkyl) using known methods, the indole nitrogen can be alkylated with R^3 if desired. Reaction conditions to alkylate the nitrogen of an indole derivative are well known to those skilled in the art and include the use of strong bases such as alkali metal hydrides, hydroxides, amides, alkoxides and alkylmetals, in the appropriate solvent (such as THF, dioxane, DME, DMF, MeCN, DMSO, alcohols and the like) at temperatures ranging from –78 °C to 140 °C. An electrophilic form of R^3 is used for the alkylation of the indole anion. Such electrophilic species include iodides, bromides, chlorides and sulfonate esters (mesylates, tosylate, brosylate or triflate).

Halogenation (usually bromination, but also iodination) of the 2-position of the indole **2(iv)** gives **2(v)**. Suitable halogenating agents include, for example, elemental bromine, *N*-bromosuccinimide, pyridine tribromide, dibromohydantoin and the corresponding iodo derivatives. Suitable solvents for this reaction are inert to reactive halogenating agents and include for example hydrocarbons, chlorinated hydrocarbons (DCM, CCl_4, $CHCl_3$), ethers (THF, DME, dioxane), acetic acid, ethyl acetate, IPA, and mixtures of these solvents. Reaction temperature ranges from –40 °C to 100 °C. A method of choice to carry out the bromination of indoles as shown in Scheme 2 was described by L. Chu (*Tet. Lett.* **1997**, *38*, 3871).

The 2-bromoindole derivatives **2(v)** can be converted directly to fully substituted key intermediates **I(v)** through a cross-coupling reaction with aryl or heteroaryl boronic acids, boronate esters or trialkylstannane derivatives. These boron or tin organometallic species are from commercial sources or can be prepared by standard literature procedures. Cross-coupling with organoboron reagents can be

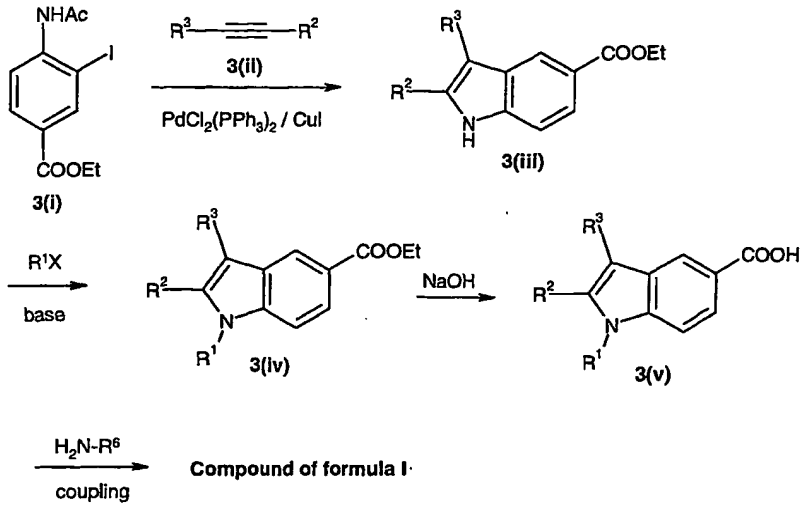
carried out by any variations of the Suzuki cross-coupling reaction reported in the literature. This usually involves the use of a transition metal catalyst (usually Pd°), triaryl or triheteroarylphosphine ligands, an additive such as an inorganic chloride (e.g. LiCl), and a base (usually an aqueous inorganic base such as sodium or potassium carbonate or phosphate). The reaction is usually carried out in an alcoholic solvent (EtOH), DME, toluene, THF and the like at temperatures ranging from 25 °C to 140 °C.

Cross-coupling with tin reagents can be carried out by any variations of the Stille cross-coupling reaction reported in the literature. This usually involves the use of a transition metal catalyst (usually Pd°), triaryl or triheteroaryl phosphine ligands, and an additive such as an inorganic chloride (e.g. LiCl) or iodide (e.g. CuI). Suitable solvents for this reaction include toluene, DMF, THF, DME and the like at temperatures ranging from 25 °C to 140 °C. Intermediate **I(v)** is then converted to compounds of formula **1** as described for Scheme 1.

Alternatively, the 2-bromoindole intermediate **2(v)** can be trans-metallated to an organotin species (or organozinc) and used in Stille-type cross-coupling reactions under conditions described above. In this case, aromatic and heteroaromatic halides (chlorides, bromides, iodides) or triflates are used to introduce R^2. The conversion of 2-bromoindole derivatives **2(v)** to the corresponding organotin species **2(vi)** is carried out via initial low-temperature (usually –78 ° to –30 °C) halogen-metal exchange using an alkyllithium reagent (e.g. nBuLi or *tert*-BuLi) or using lithium metal. The transient 2-lithioindole species is then trapped with a trialkyltin halide (e.g. nBu_3SnCl or Me_3SnCl). Alternatively, the lithioindole intermediate can be trapped with zinc chloride to form the corresponding organozincate which can also undergo transition metal-catalyzed cross-coupling with aromatic and heteroaromatic halides or triflates as described, for example, by M. Rowley (*J. Med. Chem.* **2001**, *44*, 1603).

The present invention also encompasses compounds of formula **1** where the carboxylic group is in the 5-position of the indole system. The synthesis of such compounds is based on adaptation of literature procedures and is depicted in Scheme 3:

Scheme 3



In carrying out the synthetic route illustrated in Scheme 3, ethyl 4-acetamido-3-iodobenzoate **3(i)** undergoes metal catalyzed cross-coupling with an alkyne **3(ii)** to give a 2,3-disubstituted-5-indolecarboxylate **3(iii)** according to an adaptation of a procedure described by A. Bedeschi et al. (*Tet. Lett.* **1997**, *38*, 2307). The indole derivative **3(iii)** is then alkylated on nitrogen with electrophilic R^1 groups (halides, sulfonate esters) under the action of a base such as alkali metal hydroxides, fluorides, hydrides amides, alkyllithium, phosphabases and the like, to give **3(iv).** Suitable solvents for this alkylation include DMF, DMA, DMSO, MeCN, THF, dioxane, DME and the like. Following saponification of the ester group with an alkaline solution, the resulting 5-indolecarboxylic acid derivative **3(v)** is coupled to H_2N-R^6 using an amide bond forming reagent as described previously (Scheme 1), to give compounds of formula I.

EXAMPLES

The present invention is illustrated in further detail by the following non-limiting examples. All reactions were performed in a nitrogen or argon atmosphere. Temperatures are given in degrees Celsius. Flash chromatography was performed on silica gel. Solution percentages or ratios express a volume to volume relationship, unless stated otherwise. Mass spectral analyses were recorded using electrospray mass spectrometry. Abbreviations or symbols used herein include:

EtOH: ethanol

DBU: 1,8-diazabicyclo[5.4.0]under-7-ene

BOC: *tert*-butyloxycarbonyl

Cbz: carbobenzyloxy carbonyl

^{i}PrOH: isopropanol

NMP: N-methylpyrrolidone

EDC: 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride

RNAsin: A ribonuclease inhibitor marketed by Promega Corporation

Tris: 2-amino-2-hydroxymethyl-1,3-propanediol

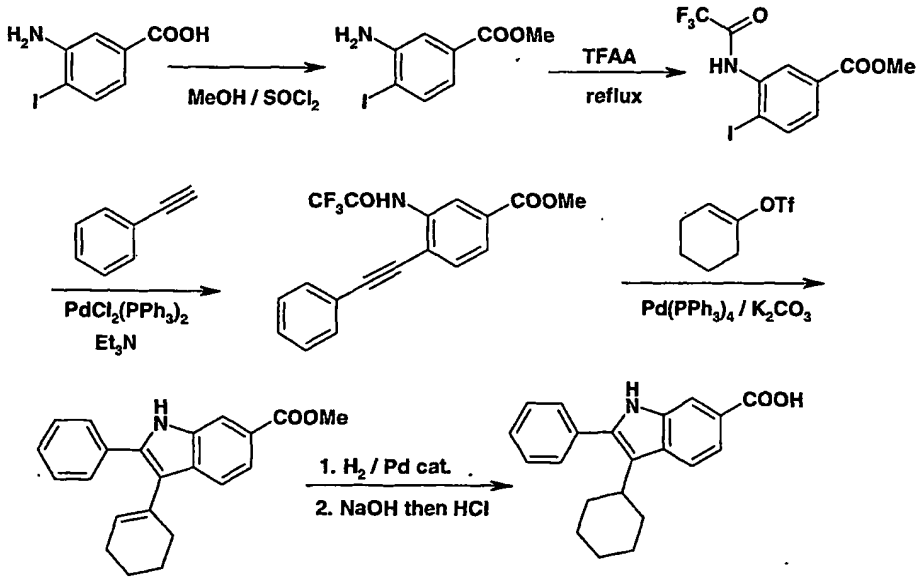
UMP: uridine 5'-monophosphate

UTP: uridine 5'-triphosphate

IPA: isopropyl acetate

Examples 1-45 illustrate methods of synthesis of representative compounds of this invention.

EXAMPLE 1



Methyl 3-amino-4-iodobenzoate:

3-Amino-4-iodobenzoic acid (13.35 g, 50.8 mmol) was added to MeOH (150mL) and $SOCl_2$ (4.8 mL, 65.8 mmol, 1.3 equivalent) was added. The mixture was refluxed for

3 h and then volatiles were removed under reduced pressure. The residue was co-evaporated three times with MeOH and dried in vacuo (15.23 g).

Methyl 3-trifluoroacetamido-4-iodobenzoate:

The aniline derivative from above (14.53 g, 52 mmol) was dissolved in DCM (200 mL) and TFAA (15 mL, 104 mmol) was added. The dark purple solution was refluxed overnight. Volatiles were removed under reduced pressure and the residue was passed through a short pad of silica gel using DCM as eluent. The desired product was obtained as a pink solid (13.81 g).

4-Phenylethynyl-3-(2,2,2-trifluoro-ethanoylamino)-benzoic acid methyl ester:

The iodide from above (0.742 g, 2 mmol), phenylacetylene (0.37 mL, 3.9 mmol, 1.7 equivalent) and Et_3N (6 mL) were charged in a dry flask under argon. $PdCl_2(PPh_3)_2$ (0.241 g, 0.3 mmol) was added and the mixture was stirred at room temperature until judged complete by HPLC analysis (~5 h). The reaction mixture was concentrated to half volume under reduced pressure and diluted with water (80 mL). The mixture was extracted with EtOAc (3 x 100 mL) and the organic extract washed with 5% HCl (100 mL), after (100 mL) and brine (40 mL). After drying over $MgSO_4$, the residue was purified by flash chromatography using 20% EtOAc – hexane as eluent to give the desired cross-coupled alkyne as a tan solid (0.442 g).

Methyl 3-(cyclohexenyl)-2-phenylindole 6-carboxylate:

A flame-dried flask was charged with finely powdered anhydrous K_2CO_3 (0.153 g, 1.1 mmol) and the alkyne derivative from above (0.390 g, 1.1 mmol). Dry DMF (4 mL) was added and the suspension degassed with a stream of argon. The enol triflate derived from cyclohexanone, prepared following the procedure described by A.G. Martinez, M. Hanack et al. (*J. Heterocyclic Chem.* **1988**, *25,* 1237 or equivalent methods described in the literature, (0.802 g, 3.3 mmol, 3 equivalents) was added followed by $Pd(PPh_3)_4$ (0.086 g, 0.07 mmol) and the mixture was stirred for 8 h at room temperature. DMF was removed under vacuum and the residue purified by flash chromatography using DCM as eluent (0.260 g).

Methyl 3-cyclohexyl-2-phenylindole-6-carboxylate:

The material from above was hydrogenated (1 atm H_2 gas) over 20% $Pd(OH)_2$ in the usual manner, using MeOH as solvent. The desired cyclohexane indole was